A Dissertation on

"A STUDY OF USEFULNESS OF PSYCHOMETRIC TESTS AND CRITICAL FLICKER FREQUENCY IN DIAGNOSIS OF MINIMAL HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CIRRHOSIS" AT GOVERNMENT STANLEY HOSPITAL, CHENNAI – 600 001.

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CERTIFICATE

This is to certify that **Dr. P.VANJI NATHAN ,** Post -Graduate Student (MAY 2011 TO APRIL 2014) in the Department of General Medicine STANLEY MEDICAL COLLEGE, Chennai- 600 001, has done this dissertation on **"A STUDY ON USEFULNESS OF PSYCHOMETRIC TESTS AND CRITICAL FLICKER FREQUENCY IN DIAGNOSIS OF MINIMALHEPATIC ENCHEPHALOPATHY IN PATIENTSWITH CIRRHOSIS" AT GOVERNMENT STANLEY HOSPITAL, CHENNAI – 600 001.** under my guidance and supervision in partial fulfillment of the regulations laid down by the Tamilnadu Dr.M.G.R. Medical University, Chennai, for M.D. (General Medicine), Degree Examination to be held in April 2013.

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DECLARATION

I, **Dr. P. VANJI NATHAN.,** declare that I carried out this work on **"A STUDY ON USEFULNESS OF PSYCHOMETRIC TESTS AND CRITICAL FLICKER FREQUENCY IN DIAGNOSIS OF MINIMALHEPATIC ENCHEPHALOPATHY IN PATIENTSWITH CIRRHOSIS" AT GOVERNMENT STANLEY HOSPITAL, CHENNAI – 600 001.** at the Medical ward and Medical GastroEnterology ward of Government Stanley Hospital during the period June 2013 to November 2013. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, or diploma to any other university, board either in India or abroad.

This is submitted to The Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfilment of the rules and regulation for the M. D. Degree examination in General Medicine.

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ABSTRACT

Background: Minimal hepatic encephalopathy (MHE) occurs in patients with cirrhosis of liver but with only subtle alterations in cognition and psychomotor functions. The aim of the study is to assess the usefulness of Psychometric tests and Critical Flicker Frequency Test (CFT) in detecting MHE .

Methods: We examined 100 patients diagnosed as cirrhosis with Psychometric tests - Number connection tests –A and B(NCT-A &B), Line Tracing Test(LTT) , Digit Symbol Test(DST), Serial Dotting Test(SDT) and Critical Flicker Frequency Test and compared the above tests with 50 normal people as controls.

Results: The sex distribution showed Male preponderance with 76% males in the study group and 64 % in the control group. Mean age of presentation is 40 years. Psychometric tests showed abnormal results with NCT- A in 17%, NCT-B in 60%, DST in 67%, LTT in 74%, DT in 70% and CFF in 73% among the study group but no significant results among the control group. Both the Psychometric tests ($p=0.000$) and Critical Flicker Frequency Test ($p=0.000$) were useful in detecting cases of Minimal Hepatic Encephalopathy in patients with cirrhosis.

Conclusion: Both the Psychometric tests and CFF tests were effective in diagnosing Minimal hepatic encephalopathy. Psychometric tests have subjective variations with consumption of more time while CFF Test is more objective in nature requiring no educational qualifications for undergoing and interpretation of the light stimulus and is highly reproducible. Hence we recommend CFF test as screening procedure in Out Patient Department to detect MHE earlier .

INTRODUCTION

Hepatic encephalopathy (HE) is a potentially reversible, metabolically caused disturbance of central nervous system function that occurs in patients with acute or chronic liver disease. It encompasses a board spectrum of neurological symptoms of varying severity and is classified according to clinical symptoms. Minimal hepatic encephalopathy (MHE), previously known as subclinical or latent hepatic encephalopathy, is at the beginning of this spectrum. MHE has a high prevalence among patients with liver cirrhosis (22% to 74%).

It is defined as HE without symptoms on clinical/neurological examination, but with deficits in some cognitive areas that can only be measured by neuropsychometric testing and critical flicker frequency test. The areas with impairments are attention, visuospatial perception, speed of information processing, especially in the psychomotor area, fine motor skills, and short-term memory leading to impaired quality of life and ability to work-associated with driving errors, accidents and further deterioration into overt encephalopathy and thereby with increased mortality. In our study, we study the effectiveness of Psychometric tests and Critical flicker frequency test in detecting minimal hepatic encephalopathy earlier in patients with cirrhosis.

AIMS AND OBJECTIVES

To study the usefulness of psychometric tests and critical flicker in diagnosing Minimal hepatic encephalopathy in patients diagnosed as cirrhosis .

REVIEW OF LITERATURE

Hepatic encephalopathy is (HE) defined as serious but reversible disturbances in the functions of central nervous system due to liver failure manifested as an alteration in cognitive function and mental status. It is one of the most common complications of cirrhosis having detrimental effects on leading a quality of life and on patient's survival. The development of HE in acute liver injury is considered as a prerequisite for a diagnosis of Fulminant hepatic failure . The underlying mechanism for the development of HE has been reported as escape of toxins derived from the gut into the systemic circulation as they are not metabolized by the liver due to shunting of blood through collaterals and also due to reduction in functioning liver tissue mass.

CLASSIFICATION OF HEPATIC ENCEPHALOPATY

Overt hepatic encephalopathy develops as a clinically apparent syndrome with varied manifestations consisting of motor and psychiatric disorders and develop over days to months(1).

Hepatic encephalopathy develops in patients with chronic liver disorders who had been normal and stable over hours to days. Such a

development of episodic and overt hepatic encephalopathy may arise in those patients frequently and intermittently(2). The patients may recover to normal with intervening episodes of encephalopathy. Sometimes few other patients may have persistence of neuropsychiatric abnormalities and remaining stable over a period of time.

Thus there exist two types of overt encephalopathy with some common clinical features. There may be varied symptoms as minimal alterations in their personality , disturbances in cognitive functions to deep state of coma. They may have behavioral changes and irritability due to changes in personality.

The mental function may be affected minimal to severe confusion and further deterioration may lead to coma. They may have constructional apraxia and alterations in the pattern of sleep is also seen . Sleepiness during day time and few other disturbances in the pattern of sleep during the night are noticed(3).

Some patients exhibit foetor hepaticus in which there occurs a musty , sour and faeculent smell like because of the Mercaptans(4).Neither its presence could correspond to the duration and severity of the hepatic encephalopathy nor the absence of mercaptans precludes the diagnosis.

Alterations in the motor system include that of disturbances in speech , rigidity and tremors (5,6) as extrapyramidal features and pyramidal features as exaggerated deep tendon reflexes with increased tone of the muscles and Positive Babinski sign(7,8) . The flapping tremors also known as Asterixis is noticed which is not specific for hepatic encephalopathy as also seen in respiratory system failure , renal failure , cardiac failure , toxicity of phenytoin and electrolyte disturbances as in hypomagnesemia.

Episodic hepatic encephalopathy

Episodic type of hepatic encephalopathy develops in patients who had stable clinical status with majority of them with an identifiable precipitating underlying cause .

Precipitating causes lead to hepatic encephalopathy by various mechanisms as by

1) Rise in Nitrogenous end products,

2) Affecting and causing depression of functions of brain and liver. The patients with overt hepatic encephalopathy may recover from encephalopathy with the visibly improving clinical condition earlier than improvements appearing in Electroencephalogram and in Psychometric tests(24).

Still there remains some impairments affecting those of cognitive , neuropsychiatric functions commonly encountered with either through sugery or larger spontaneously created portosystemic shunts, and with sever decompensation of the underlying chronic liver disease

PRECIPITATING CAUSES OF HEPATIC ENCEPHALOPATHY

Gastrointestinal bleeding
Sepsis
Electrolyte imbalance
Hyponatraemia
Hypokalaemia
Dehydration
Fluid restriction
Excessive diuresis
Paracentesis
Diarrhoea/ vomiting
Constipation
Excess protein load
Alcohol misuse
CNS-active drugs
TIPS insertion
Surgery

TIPS, transjugular intrahepatic portal–systemic shunt.

Persistent hepatic encephalopathy

Few patients with chronic liver disorders will exhibit persistence of features of encephalopathy but with stable clinical status and often with significant portosystemic shunt .

There may not be alterations in the level of consciousness but increased severity of these pre existing symptoms . In addition, there may be marked rigidity, unintentional fine tremors, with a shuffling gait and

speech of staccato type . Its diagnosis is often missed as there may not be clear presence of biochemical alterations and other clinical features .

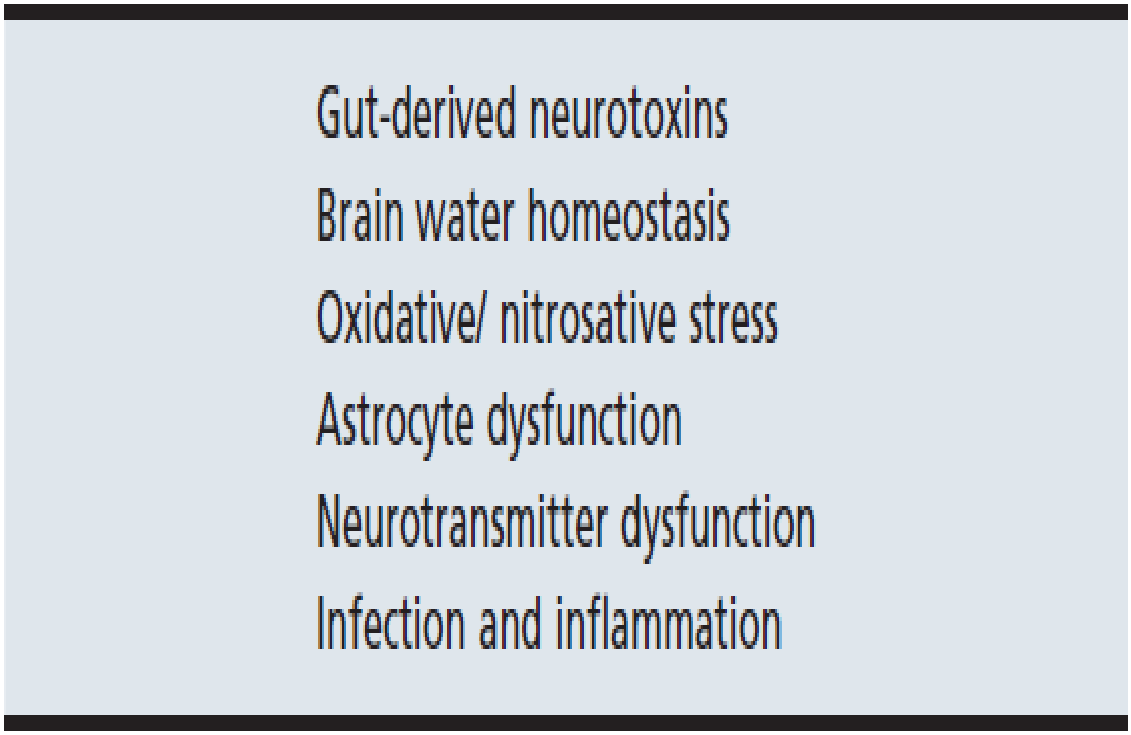
Minimal hepatic encephalopathy

This group consists of patients with cirrhosis and normal clinical status but still with impairment of cognition and motor functions (12, 27) . Minimal hepatic encephalopathy severely affects the complex tasks (30, 31) as in the case of driving skills and impairs the quality of life (28, 29) and needs to be diagnosed earlier without which it may progress to Overt type of encephalopathy (32, 33, 34).

Pathogenesis

The pathogenesis in HE is highly controversial and several theories have been put forth in the past. Two most essential factors namely as failure of the liver and shunting of portosystemic circulation have been identified for the development of Hepatic encephalopathy . There are some instances wherein shunting of portosystemic circulation with the preservation of liver functions does not result in the development of hepatic encephalopathy.

There are several changes associated with the development of Hepatic encephalopathy



Neurotoxins derived from the intestines

Various neurotoxins have been found to be derived from the intestines and are associated with the development of Hepatic encephalopathy amongst which Ammonia is considered to play a key role.

Synthesis of Ammonia takes place

1) From the proteins contained in the diet ,

2) By the action of colonic bacteria ,

3) By the deamination action of Glutaminase on Glutamine .

The ammonia thus formed are absorbed and attains higher concentrations in the Portal venous blood. The liver cells absorb ammonia and convert it to urea through the reactions in Urea cycle.

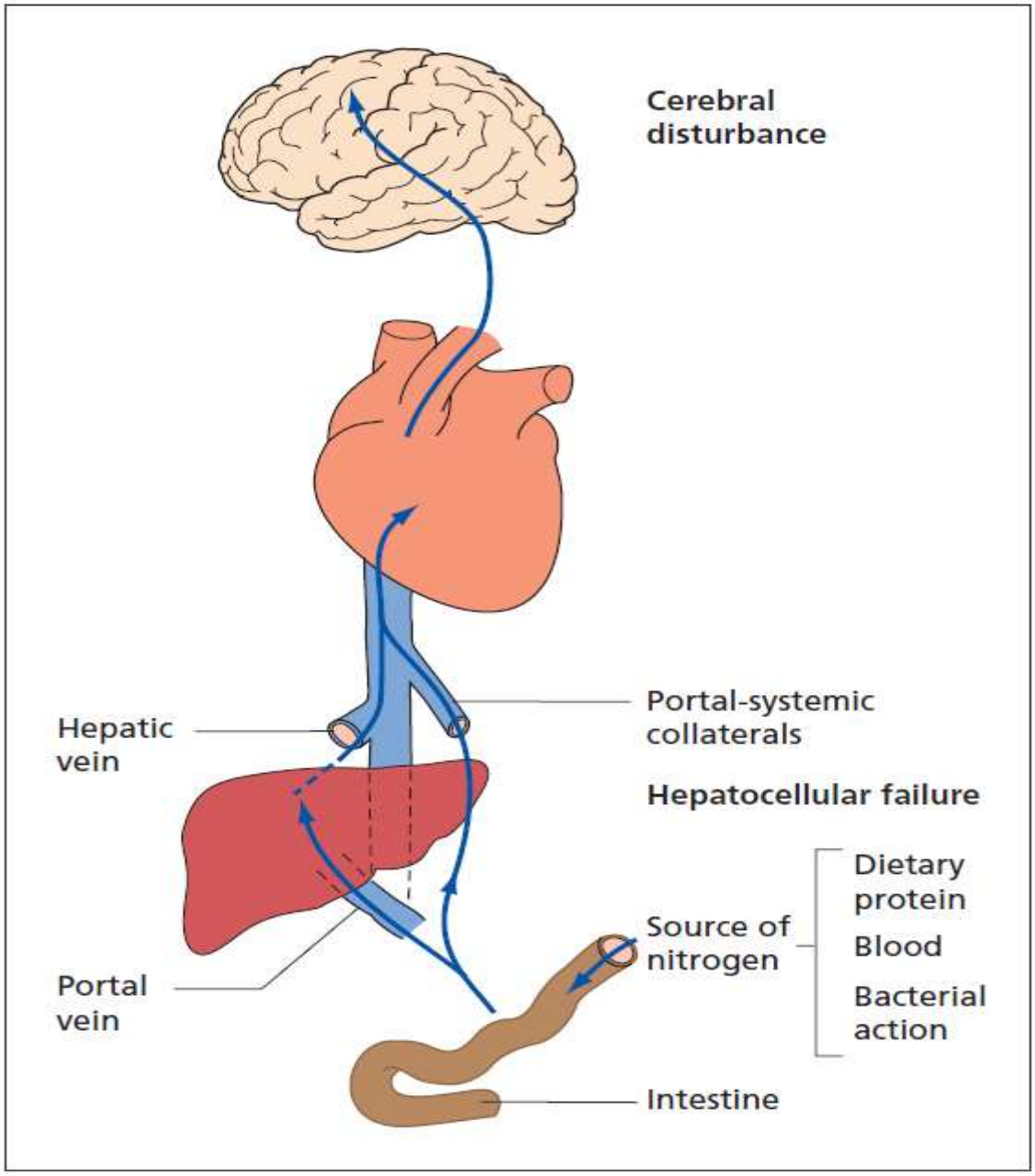
The level of ammonia in the blood is raised in the following instances.

a) Due to the increased flow of blood through the splanchnic circulation secondary to portal hypertension favouring the increased absorption of ammonia

b) Due to decrease in liver mass with retained functions .

c) Increased colonization of intestines with urea splitting enzyme Urease leading to increased synthesis of ammonia in the bowel .

d) Due to reduced mass of muscle in patients with cirrhosis resulting in reduction of metabolism of ammonia in the muscle .



The uptake of ammonia by the brain is enhanced in patients with cirrhosis (35). Notably urea cycle does not take place in the brain . Ammonia is found to have detrimental effects on the astrocytes with marked predilection for Basal ganglia, cerebellum and cortex of the cerebrum .The neurons located in the cortex of the cerebrum are also significantly(36) .

There is a poor correlation between the levels of ammonia in the blood and the severity of the impairment in cognitive and motor functions .Few more neurotoxins found to be in association with the development of hepatic encephalopathy are

a) Mercaptans

b) fatty acids with short and medium chains

c) Indoles

d) Phenols

The above said toxins are said to exhibit their toxicity on the functions of cortical neurons either directly or with synergistic action along with ammonia leading to the development of hepatic encephalopathy.

Homeostasis of Brain water

Entry of ammonia into the central nervous system leading to increased concentrations of glutamine which is osmotically active thereby causing the swelling of Astrocytes. To neutralize the increased concentrations of osmotically active glutamine, astrocytes drive away few other substances which are osmotically active .Despite the above , cerebral edema of low grade develops which had been demonstrated with the help

of Diffusion transfer Magnetic Resonance techniques of imaging (37,38) and Cerebral Magnetization techniques. There also exists a fair amount of correlation between the degree of severity of HE and the changes noticed during Cerebral 1H-Magnetic Resonance Spectroscopy(39,40) . A small increase in the water content of astrocyte although would not rise the intracranial tension but will impair the functions of the brain. Along with Ammonia , few other contributing factors like Benzodiazepines , hyponatremia and other inflammatory mediators also result in cerebral oedema of low grade .

Oxidative/ nitrosative stress [41]

Available evidences from studies conducted in experimental animal models substantiates the role of oxidative/ nitrosative stress in the development of hepatic encephalopathy. When there is a loss of balance between the generation of Oxygen derived free radicles , Nitric oxide free radicles and the antioxidant system in the form of scavenging the free radicles , there occurs the Oxidative/ nitrosative stress .If the free radicles generated in excess lead to cellular damage and its death .

Various inflammatory mediators , swelling of astrocytes secondary to osmotic changes , Benzodiazepines and ammonia lead to generation of Oxygen derived free radicles and Nitric oxide species through *N* methyl d aspartate glutamate receptors by yet unidentified mechanism

Activation of extracellularly regulated protein kinases
Up-regulation of peripheral benzodiazepine receptors
Modulation of amino acid transport
Elevation of intracellular calcium concentrations
Release of cellular taurine → affects synaptic plasticity and GABAergic tone
Modulation of multiple ion channels
Increased pH in endocytotic vesicles → affects receptor/ ligand sorting and neurotransmitter processing
Stimulation of glycogen synthesis
Activation of NMDA glutamate receptor
Induction of oxidative/ nitrosative stress
Predisposes to neuronal dysfunction

NMDA, *N*-methyl D-aspartate.

There appears an inter relationship between oxidative stress , astrocyte swelling, and activation of NMDA receptor. Swelling of astrocytes leads to oxidative stress via NMDA receptor activation and Calcium ions dependent steps which results in further swelling of astrocytes in a viscious cycle.

Dysfunction of Astrocytes

Swelling of astrocytes and oxidative stress impair the functions of astrocytes in patients with hepatic encephalopathy. The tyrosine residues in the proteins of the astrocytes undergo covalent modification and nitration of tyrosine residues takes place. This type of modification impairs the function of the protein and also affect the signal transduction of the astrocytes adjacent to the blood brain barrier and hence the transport of substrate inside the astrocytes .The reaction of nitration of proteins may not involve all proteins thereby permeability of the blood brain barrier getting affected selectively .

The free radicles derived from oxygen causes oxidation of RNA affecting the processes of protein synthesis resulting in the formation of unstable and defective proteins .Consequently , receptors for neurotransmitters are synthesized and assembled defectively impairing the neurotransmission. Zinc is mobilized from proteins due to nitric oxide

derived free radicles and zinc ions impair the functions of several enzymes .Zinc also reduces the uptake of Glutamate and enhances the GABAergic neurotransmission .

The functions of Astrocytes are directly impaired by Ammonia by resulting in the alterations in the transport, metabolism of neurotransmitters [42] , transduction of intra-cellular signals , and genetic expression . The above changes in functions of astrocytes eventually culminates in the impairment of plasticity of the synapse, slowing of oscillatory neuronal activity and disruption of glioneuronal communication .

Alterations in cerebral neurotransmission

Several neurotransmitters are affected in these patients with a gain of upper hand for the inhibitory system over the excitatory system due to an increase in the tone of GABAergic system .

Glutamate

The chief excitatory neurotransmitter in the central nervous system is Glutamate and is produced in the presynaptic neurons and contained in the storage vesicles.

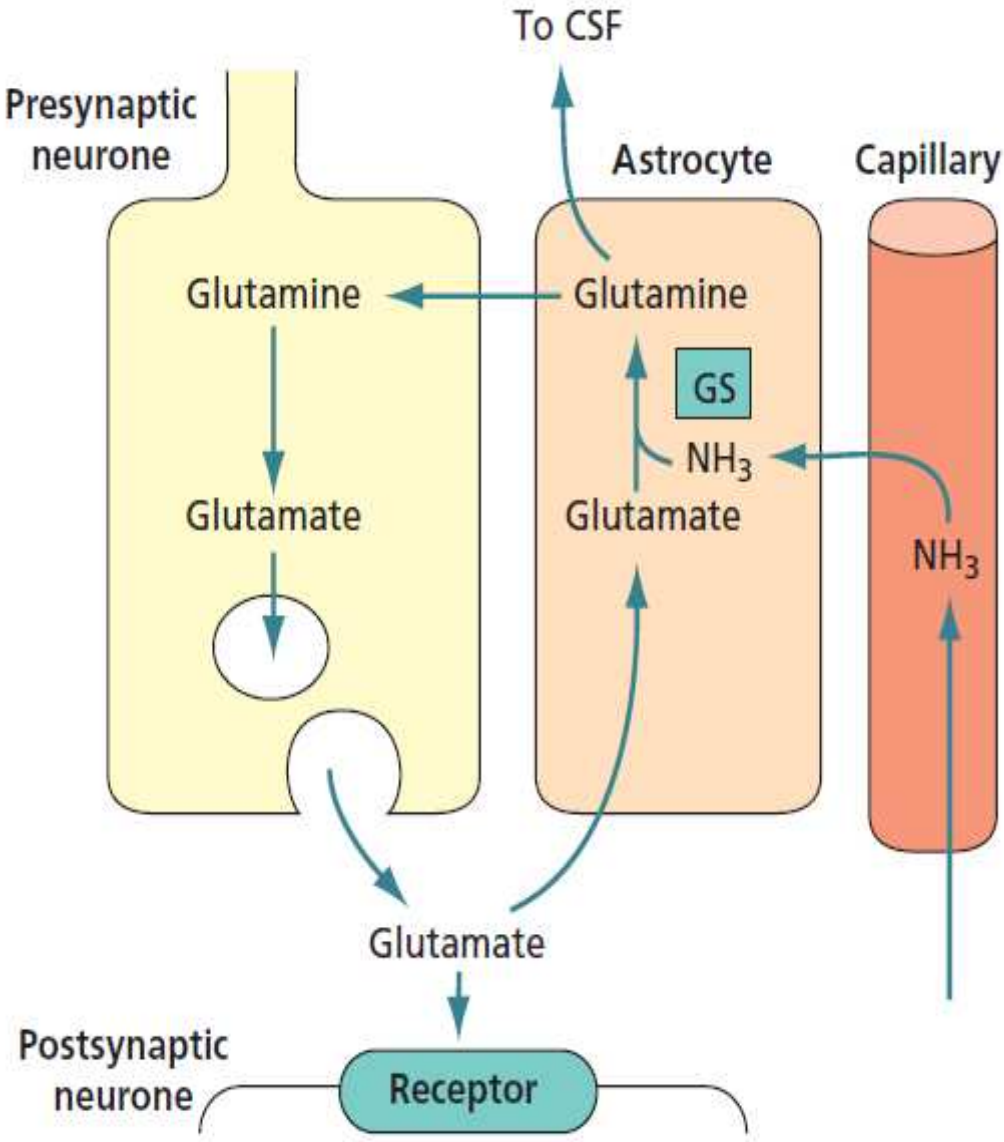
Following its release into the synaptic cleft , reuptake of glutamate into the astrocytes occur where it combines with ammonia to yield glutamine in the presence of an enzyme Glutamine synthetase.

Subsequently , transportation of glutamine to the presynaptic nerve terminals is carried out and converted back to glutamate. Glutamate levels in the brain are reduced in these patients as it is utilized in its conversion to glutamine with the availability of excess ammonia. Paradoxically the levels of glutamate in the CSF and ECF are raised due to release from the astrocytes following its swelling and defective reuptake . Ammonia plays a role in the reduction of receptors for glutamate over the membranes of neurons and astrocytes (43,44).

γ - Aminobutyric acid and the neurosteroid system(45)

The main neurotransmitter with inhibitory function in the central nervous system is Gamma Amino butyric acid . The receptor for GABA consists of a complex structure with regions for binding with Barbiturates, Neurosteroids and Benzodiazepines which after binding causes inward flow of chloride ions . Consequently there occurs hyperpolarization and further inhibition .

It has been found out that GABA-ergic activity is increased in patients with hepatic encephalopathy . Several compounds have been reported with neurotoxicity that include Neurosteroids , ligands with action similar to Benzodiazepine and Ammonia . They were found to have modulatory effects on the function of GABA receptor . There are few Neurosteroids thought to be produced in the astrocytes of the central nervous system that include Allopregnanolone which causes increased GABAergic activity in patients with hepatic encephalopathy .



It has been found out that in the brains of patients died due to hepatic coma levels of allopregnanolone is raised . Neurosteroids have been found to potentiate the toxic effects of Ammonia on the central nervous system by their modulatory effects on the GABA receptor thereby increasing inhibitory action.

They are also produced in the gonads, adrenals and kidneys with their levels raised in patients with failure of the Hepatic functions .Chemically , neurosteroids are lipid soluble reflecting their ability to cross the BBB and resulting in the effects of inhibition . The levels of the precursors of neurosteroids are also elevated in liver failure.

They also impair the effects of Glycine ,NMDA , Opioids and 5-hydroxy tryptamine in patients affected with hepatic failure . Neurosteroids can affect the processes of Transcription thereby impairing the coding for the synthesis of various receptors and other proteins in the central nervous system .

The critical role of GABA system in the development of encephalopathy is also proven by the raised sensitivity to Benzodiazepines (23) and over the fact that few patients got some improvement on treating them with Flumazenil having antagonistic effects on receptors of Benzodiazepine(46) .

Serotonin

Serotonin (5 - hydroxytryptamine;5 - HT) is a neurotransmitter with exerting their actions for the maintenance of consciousness and the cortical arousal. The enzyme MonoAmine Oxidase A [MAO-A] is involved in the metabolism of Serotonin (47) and its concentration is increased in the blood accompanied with a raise in its receptors(49) in these patients .

Also, the levels of its metabolites as 5-OH Indole acetic acid is raised in the brain tissues . Antagonist of serotonin namely Ketanserin is used for the treatment of portal hypertension(50) and its utility in this condition confirms the role played by the Serotonin in the development of hepatic encephalopathy .

Dopamine

Another neurotransmitter namely Dopamine serves the functions of attention , mood, learning, behavior , motivation, and cognition voluntary movement . The enzyme involved in the clearance of Dopamine namely MonoAmineOxidase (51) is raised along with the byproducts like Homovanillic acid levels (48) in the brain tissue .Contrary

to these , Dopamine receptors are reduced (52) and further resulting in its depletion leads to features characteristic of Parkinsonism .

The toxicity of Manganese is characterized by its accumulation in the globus pallidus and the caudate nucleus revealed in the Magnetic Resonance Imaging .Such patients exhibit features of Extra-pyramidal disorders and hence those features of Extra-pyramidal disorders are experienced by these patients .Also these patients get improvement following the treatment with Bromocriptine and other agonists of the Dopaminergic system confirming the role of Dopamine and its system in hepatic encephalopathy .

Few other systems of neurotransmitter like Opioids system and Histamine neurotransmitter systems have also been reported to be altered in these patients .

There are some reports indicating the involvement of Adenosine and AcetylCholine systems with a decrease in the AcetylCholine due to raised functions of its metabolizing enzyme AcetylCholine Esterase .

Acetylcholine acts through 1) Nicotinic receptors causing excitation while through 2) muscarinic receptors leading to the inhibition of transmission of GABA system .

The density of receptors for Nicotinic system is reduced and that of binding affinity of ACh for muscarinic receptors is also reduced thereby an increased activity of GABA egic inhibition . One of the reversible AntiCholine Esterase Antagonist as Rivastigmine is effective in the treatment of these patients pointing to the involvement of Ach system .

Further, the adenosine system is also affected and alterd thereby impairing the balance between excitatory and inhibitory systems of neurotransmission .

Inflammation and infection(67)

There will be immunocompromised state in cirrhotic patients with diminished capability of Macrophages and Neutrophils to eliminate the infectious pathogens .There occurs endotoxemia for prolonged duration of time secondary to the transmigration of the bacteria and poses risk for infection .Such infections can lead to the development of hepatic encephalopathy .There occurs a combination of infection which is developed by an infectious pathogen and inflammation – a complex response initiated by the cells and tissues in response to an injurious stimuli leading to the formation of inflammatory mediators. Both the

inflammation and infection can occur together resulting in the tissue damage .

Two essential parts of Blood brain barrier as Endothelial cells and astrocytes participate in the systemic inflammation with the release of several inflammatory mediators and also affecting the neurotransmitter systems .

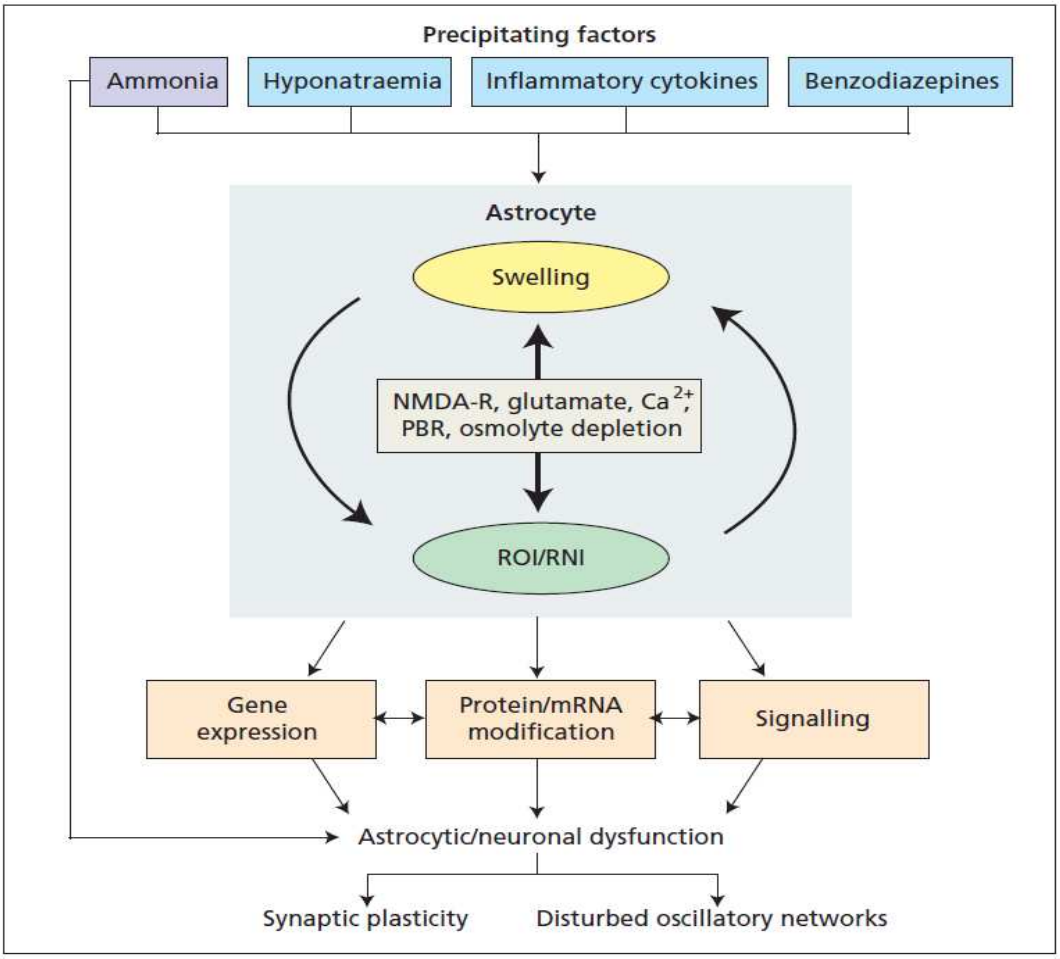
There occurs defects in the functions of Neutrophils caused by ammonia and subsequently with the generation of Oxygen derived free radicles . These free radicles lead to the cellular injury and inflammation with the resultant ineffective Neutrophils in dealing with the infectious organism and deterioration of the effects of ammonia over the brain .

Therefore ,the participation of neutrophil and the endothelial interaction in the microcirculation of the brain leads to the migration of the Neutrophils across the blood brain barrier and then results in the release of inflammatory mediators and eventually free radicle induced swelling and damage of the Astrocytes .These above said processes are facilitated with increased Ammonia levels and endotoxemia of chronic duration causing further deterioration and damage to the Astrocytes and neuronal tissues .The concept of giving Probiotics reducing the incidence

of intestinal translocation of gut bacteria strengthens the role of infection and further inflammation in the precipitation of encephalopathy .

An unified hypothesis for hepatic encephalopathy

The bypass of Ammonia leaves it detoxified , gains access into the systemic circulation and on reaching the brain exerts its neurotoxic effects on the brain tissues wherein causes swelling of Astrocytes through glutamine and glutamate



reactions .Then it causes cerebral edema of low grade in severity . Swelling of the Astrocytes results in the generation of free radicles derived from Oxygen and Nitric oxide and further altering the homeostasis of water in the brain tissues due to toxicity of Ammonia . In addition to the above, there occurs impairment of signal transduction intracellularly, altered genetic expressions , covalent modification of proteins and nuclear material and impaired neurotransmission .These further impairs the communication between the neural tissues and affecting the plasticity of the synapse . Constipation , GI bleeding and increased dietary intake of protein can lead to the precipitation of encephalopathy due to associated raised levels of Ammonia .Besides the above proinflammatory mediators , Benzodiazepines and reduction in the serum Sodium levels have also been implicated in the development of encephalopathy.

Cirrhosis of liver

Hepatic encephalopathy is develops in Cirrhosis of liver . Cirrhosis of liver, irrespective of the underlying cause, is characterized by the presence of fibrosis along with regenerating nodules thereby leading to the distortion of architecture of hepatocellular structure . Laennec coined the Greek term, Schirrus referring to tawny or orange coloured liver surface seen at the time of autopsy. Previously there was a thought that cirrhosis is irreversible but now it is considered that once the underlying cause or

insult is removed then fibrosis of liver becomes reversible. There have been various causes enumerated to cause cirrhosis as in the following table classified based on their etiology.

Causes of Cirrhosis :

1)Alcoholism

2)Chronic viral hepatitis

Hepatits B

Hepatitis C

3)Non alcoholic steatohepatitis

4)Autoimmune hepatitis

5)Biliary cirrhosis

Primary Biliary Cirrhosis

Primary sclerosing cholangitis

Autoimmune cholangiopathy

6) Metabolic causes

Haemochromatosis

Wilson’s disease

Cystic Fibrosis

Alpha-1 antiyrypsin deficiency

Galactosemia

Tyrosinosis

Type IV Glycogen storage disorder

Hereditary Fructose Intolerance

7)Hepatic venous outflow obstruction

Budd chiari syndrome

Veno-occlusive disease

8) Drugs and Toxins – Amiodarone , Methotrexate ,

9) Schistosomiasis

10) Indian childhood cirrhosis

11) Right Heart failure – chronic

12) Cryptogenic cirrhosis

Liver consists of several hepatic lobules of one cell thickness with the intervening sinusoids .The fenestrated endothelial cells line a basement membrane which separates the sinusoidal lumen from the space of Disse which separates the hepatocytes from the sinusoidal endothelium.

In the space of Disse , Stellate cells lie with the attachment to the basement membrane. Kupffer cells are seen adhered on to the surface of the fenestrated endothelium facing the sinusoids.

The movement of the nutrients and other molecules occur by passing through the fenestrae of the wall of the sinusoid and across the Space of Disse thereby reaching the basal surface of the hepatocytes . Such a transport of nutrient molecules are deranged by changes in the extracellular matrix and the cells subsequent to liver injuries .

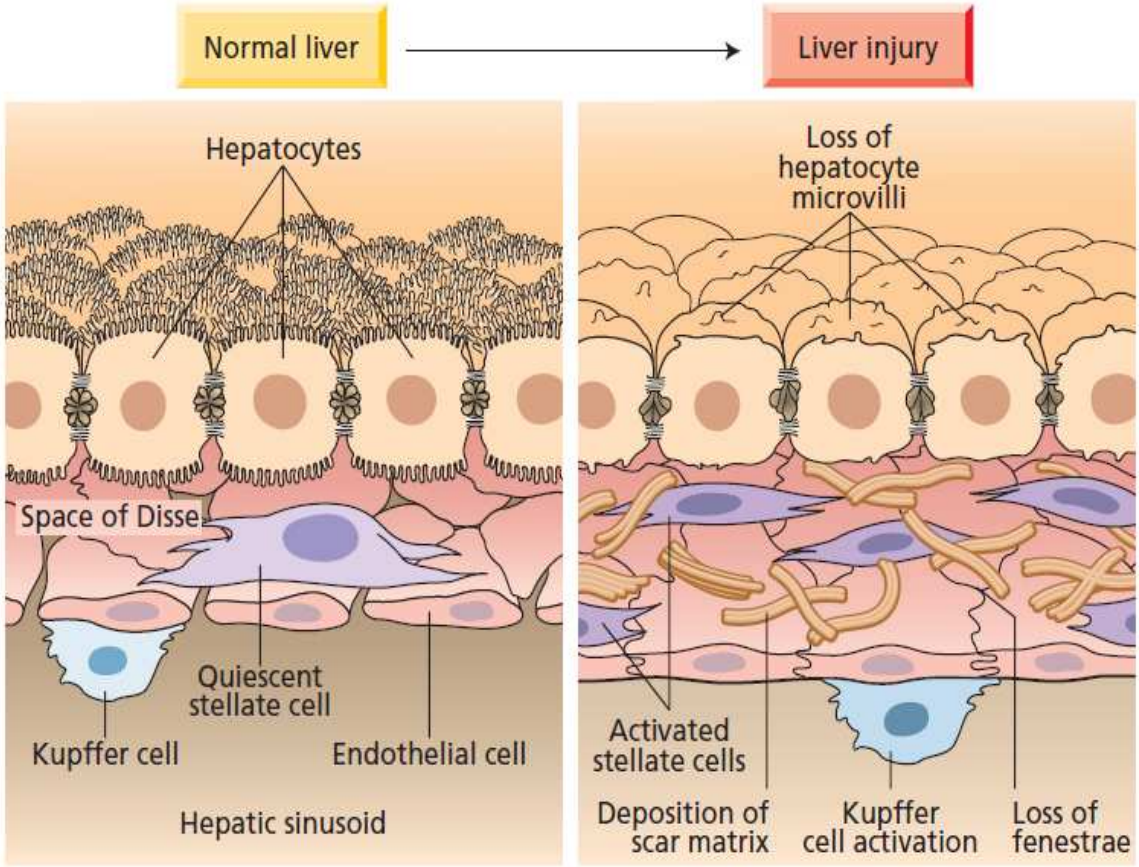


Fig.A Fig.B

A)Normal relationship between cells and matrix between hepatocytes and sinusoids B) After injury of liver

Normally in the liver , the connective tissue matrix contains Non fibrillary collagen of type IV , Proteoglycans as Heparan sulphate and Glycoproteins as Fibronectin , Laminin which all constitute the Low density basement membrane in the space of Disse. They form a lattice like matrix providing the cellular support and molecular signals essential for carrying out the differentiated functions of cells and thus allowing the transport of solutes and growth factors to take place across the basement membrane between hepatocytes and sinusoid .

After the liver injury has occurred , extracellular matrix increases to 3to 8 folds and is now composed mostly of high density interstitial fibril - forming collagens as types I and III, rather than type IV in addition to hyaluronic acid , fibronectin, and other matrix proteoglycans.

Besides the above changes , endothelial cell fenestrations and hepatocyte microvilli are lost resulting in ‘ capillarization ’ of sinusoids, and thereby impeding the metabolic exchange between the hepatocytes and the blood .Subsequently , collagen of type 1 fibers accumulates gradually due to decreased degradation and increased synthesis considered as the hallmark of fibrosis.

The principal cell involved in fibrosis is the Stellate cells present within the Space of Disse . It is also known as Ito cell , Pericyte , Fat storing cell . Ito cells remain in direct contact with endothelial cells, hepatocytes and inflammatory cells . Normally, stellate cells have intracellular droplets comprised of vitamin A. It contains 40 – 70% of the total body stores of retinoids in the liver.

The stellate cells produces predominantly type IV collagen during the quiescent stage which is the characteristic type of collagen found in a basement membrane normally . It undergoes a few changes following an injury , in its phenotype referred to as ‘ activation ’ characterized by cellular proliferation, increased contractility with expression of smooth muscle specific α – actin , secretion of proteinases degrading the matrix and synthesis of collagen of type I being the characteristic feature of cirrhosis of liver .

The activation of stellate cells is considered to be an important step in the development of hepatic fibrosis and it takes place in two steps as

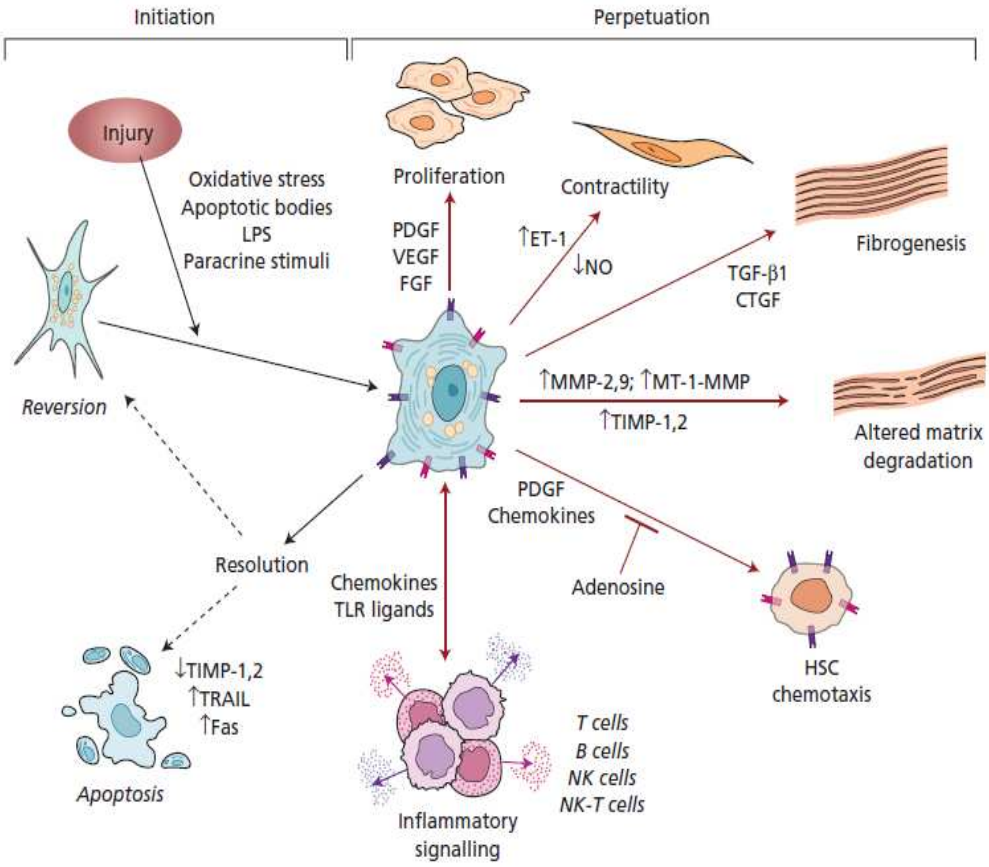
A) Initiation

B) Perpetuation

During the Initiation phase, early events take place as rapid changes in phenotype of the stellate cell and genetic expression thereby enhancing the responses chemokines , cytokines and other stimuli like reactive oxygen intermediates and lipopolysaccharide .

As a sequelae to the liver injury , there occurs the alterations in composition of in the extracellular matrix thus affecting the homeostasis of adjacent cells such as hepatocytes, sinusoidal endothelium , Kupffer cells and thereby causing stimulation in a paracrine fashion which prime the stellate cells so as to respond to cytokines and growth factors .

Perpetuation is the step characterized by the occurrence of cellular events which amplify the activated phenotype of Stellate cells and achieving certain features that are essentially crucial for the subsequent development of fibrosis. Further there occurs the enhanced proliferation of stellate cells , their contractile properties , fibrogenesis , chemotaxis of stellate cells ,secretion of Inflammatory mediators and resulting in the altered degradation of extracellular matrix.



When the injurious stimuli that initiated the liver injury is removed as in the case of Chronic alcoholism discontinuation of hepatotoxins such as ethanol or treatment of underlying liver disease, Stellate cells undergo either apoptosis or programmed cell death or reverting back to the quiescent phenotype .

Proliferation of Stellate cell

Following the stimulation of stellate cells , they undergo proliferation rapidly. The most potent mitogenic factor for Stellate cells is Platelet derived growth factor (PDGF - β) which acts through its receptor, β -PDGFR[7] .

Still few other inflammators like vascular endothelial growth factor (VEGF), Transforming growth factor - α (TGF - α), Thrombin , Endothelial growth factor (EGF), insulin - like growth factor IGF - 1 and fibroblast growth factor (FGF) are implicated as mitogens for stellate cells in the above processes.

Acquirement of Contractility in Stellate cells

After injury to the liver , the quiescent stellate cells sooner acquire smooth muscle features leading to the expression of alpha smooth muscle actin [53] and myosin [54] , conferring on them with properties of contractility.

Considering the location of stellate cells in the space of Disse, their properties of contractility leading to increase in the portal resistance that can occur even with early stages of fibrosis .Such an increased portal pressure remains reversible than that due to thickened septae and distortion of hepatic lobular architecture occurring in the more advanced stages of fibrosis .

The chief regulators of the contractility of stellate cells are Endothelin – 1 (ET-1) and Nitric oxide (NO) with mutually opposing

actions. Various other factors include Angiotensin II , Atrial Naturetic Peptide (ANP), Eicosanoids, and Somatostatin .

Fibrosis

Synthesis of type I collagen is the characteristic feature of the activated Stellate cells . TGF - β 1 is the chief and a powerful fibrogenic cytokine for the synthesis of type1 collagen by Stellate cells in addition to other cytokines like Vascular Endothelial Growth Factor, Connective Tissue Growth Factor , and Fibroblast Growth Factor . TGF - β 1 is secreted by endothelial cells lining the sinusoids, Hepatic Macrophages and Stellate cells in both autocrine and paracrine fashion thereby leading to fibrosis.

Chemotaxis

Stellate cells migrate to the inflammatory region in response to the chemoattractants, like PDGF [18] , monocyte chemotactic protein - 1 (MCP -1) and CXCR3 ligands. This migration of the stellate cells also aid in enhancing further interactions with other inflammatory cells.This ability to migrate to sites of injury may also be important for interactions

with the immune system. In addition, there occurs an alteration in the between the production and breakdown of matrix thus resulting in fibrosis

Clinical Features of HE

Development of an acute confusional state with impaired mental status, fetor hepaticus , neuromuscular abnormalities and hyperventilation . The clinical features are fluctuating with varying from mild confusion to deep coma but abrupt onset and developing over hours to days in these patients .

They may not exhibit significant neurological symptoms before the development of the acute episode except in those who had Persistent hepatic encephalopathy .

The progression of an acute episode tends to parallel the course of liver function or the removal of the precipitating factor. Prolonged episodes of HE occur among patients with terminal liver failure.

Patients usually recover from HE without major neurologic deficits and are able to return to previous activities. Impairment of consciousness initially manifests as subtle changes of personality or disturbances in the

circadian rhythm of sleep and wakefulness (i.e., insomnia during the night, somnolence during the day).

As HE progresses, the manifestations include inappropriate behavior, disorientation, confusion, slurred speech, stupor, and coma. Some patients may experience nausea and vomiting, especially if there is rapid evolution into coma.

Asterixis is a characteristic feature of HE that represents the failure to actively maintain posture or position . Asterixis is caused by abnormal function of diencephalic motor centers that regulate the tone of the agonist and antagonist muscles normally involved in maintaining posture .

The classic method of eliciting asterixis is by dorsiflexion of the patient's hand, with the arms outstretched and fingers separated. The postural lapse that occurs consists of a series of rapid, involuntary, flexion–extension movements of the wrist.

DIAGNOSIS

In a known case of a patient with cirrhosis , bleeding of Gastrointestinal Tract presenting with altered sensorium and Flapping tremors on clinical examination then it there will be no difficulty in diagnosing as a case of hepatic encephalopathy.

Sometimes, there may not be the availability of documents regarding the past history and a precipitating event of encephalopathy may not be clinically evident .Therefore the diagnosis may not be arrived at earlier and the due therapy is delayed . There is a drawback in diagnosing the condition as there is no investigation available at present as a gold standard and earmarked as to label the patient as with hepatic encephalopathy.

Availability of fewer individual tests to assess the function of the brain make it a possibility to utilize them as individually and combined to get more informations to diagnose the encephalopathy .Such tests available as Mental State Assessment

- NeuroPsychometric tests
- Neuroimaging modalities

- ElectroEncephaloGraphy and
- Sensory and Cognitive Evoked Potentials .

Examination of the Neurological system including Mental State Assessment

To exclude or to diagnose the presentation of Clinically apparent or also called as Overt encephalopathy following factors are considered(35) .

A) a need for a carefully taken and elaborated neuropsychiatric history and further aided with examination, with a specific focus on mental state changes as concentration, cognition , consciousness, memory and quality of life;

B) to utilize the two systems of grading to examine the mental status are

1) The West Haven criteria based on alterations of Intellectual function , behaviour, consciousness (36)

2) The GCS -Glasgow Coma Scale.

Few more tests are available in the form of

- Hodkinson Mental State Test,
- Mini Mental Score Test

as these tests are used for these patients widely.

C) a need for a comprehensively done neurological examination in order to observe for very subtle motor abnormalities, in the form of dysarthria, diminished speed or difficulty in implementing the rapid and also the alternating movements, raised tone, increased DTR , ataxia , impaired postural reflexes and few other abnormal movements manifesting in the form of tremors, specifically as Flapping Tremors ; association of any localized signs or sensory disturbances features ,then we have to look for alternative or other diagnoses;

West Haven Grading of HE

Grade	Features
0	No abnormalities detected
I	Trivial lack of awareness
	Euphoria or anxiety
	Shortened attention span
	Impairment of addition or subtraction
II	Lethargy or apathy
	Disorientation for time
	Obvious personality change
	Inappropriate behaviour
III	Somnolence to semi-stupor
	Responsive to stimuli
	Confused
	Gross disorientation
	Bizarre behaviour
IV	Coma, unable to test mental state

D) we have to look for and also to exclude the presence of any organic causes like subdural haematoma, intoxication with alcohol or toxicity of drugs **,** Wernicke ' s encephalopathy, metabolic abnormalities associated with diabetes mellitus and renal insufficiency or failure.

There requires elicitation of history from the patient's relatives and other friends to correlate the history and to ask for the changes noticed in the patient's mental state before the illness.

Psychometric Tests

Psychometric Tests are used to recognize the Minimal hepatic encephalopathy with impairment of psychometric functions in cirrhotic patients with clinically stable status .

Psychometric tests help us in assessing the severity of the disease in the patients with obviously appearing impairment in an objective manner . Minimal hepatic encephalopathy alters the psychometric functions which are reflected in the Psychometric tests in the form of defective visuo-spatial abilities, fine motor skills , and attention when compared to other cognitive capabilities which are relatively retained .

On the other hand , Overt hepatic encephalopathy reveals few more defects in abilities of concentration psychomotor speed, and other functions of execution . Over the decades , there were several efforts made at simplify and to have a simple yet comprehensive set of tests dependent on their ability to detect the alterations in the Psychological and Motor functions . It is of practical experience to notice that instead of a single test ,a battery of investigations are of more helpful in detecting such alterations .

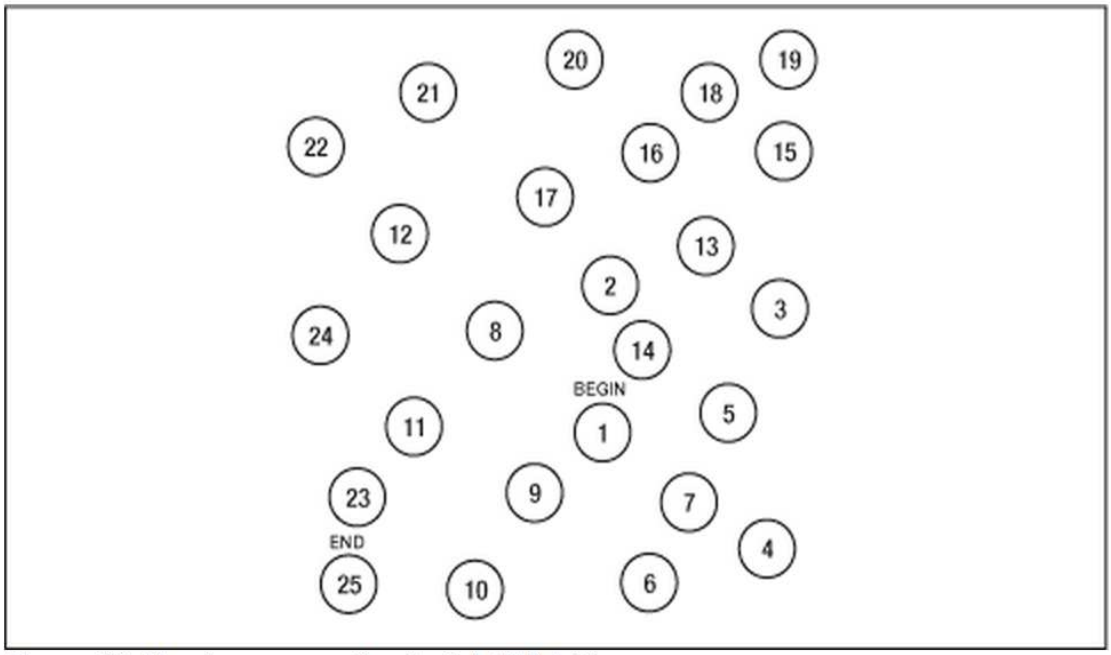


Figure 16. Number connection test A (NCT-A).

Psychometric tests are also known as Paper and Pencil Tests and comprise the following tests employed for these patients .

1) Number Connection Test A

2) Number Connection Test B

3) Digit Symbol Test (12)

4) Serial Dotting Test

5) Line Tracing Test

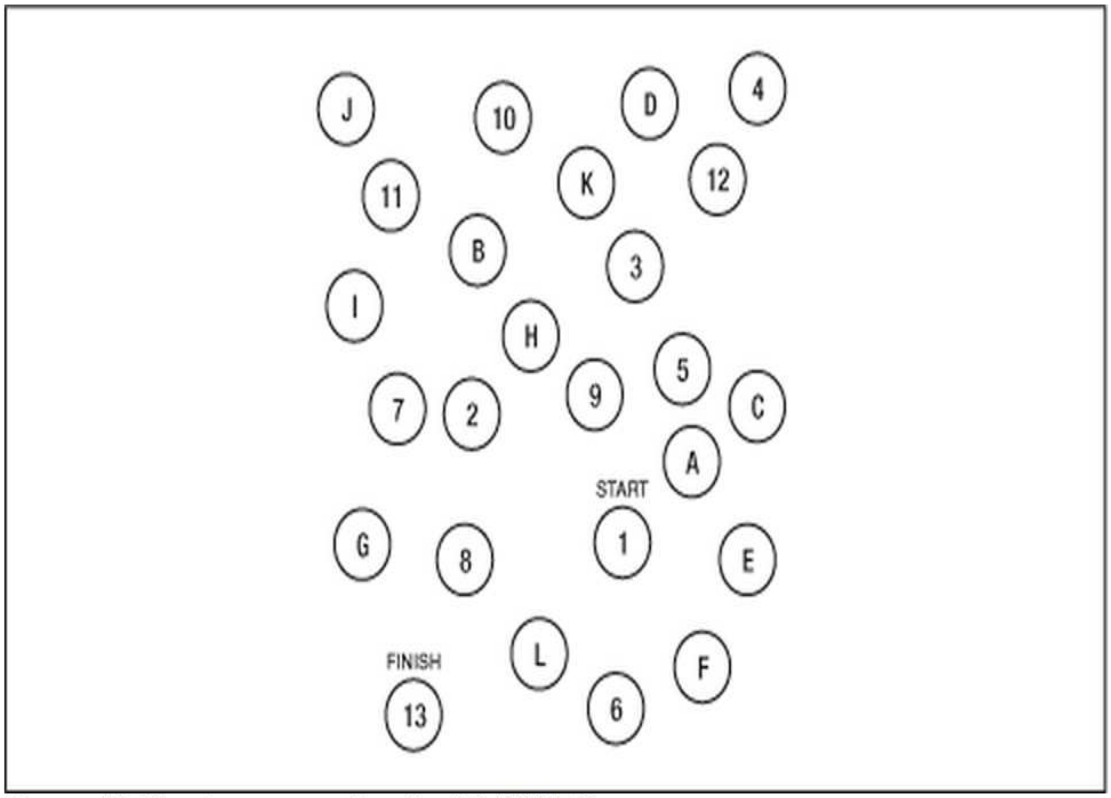
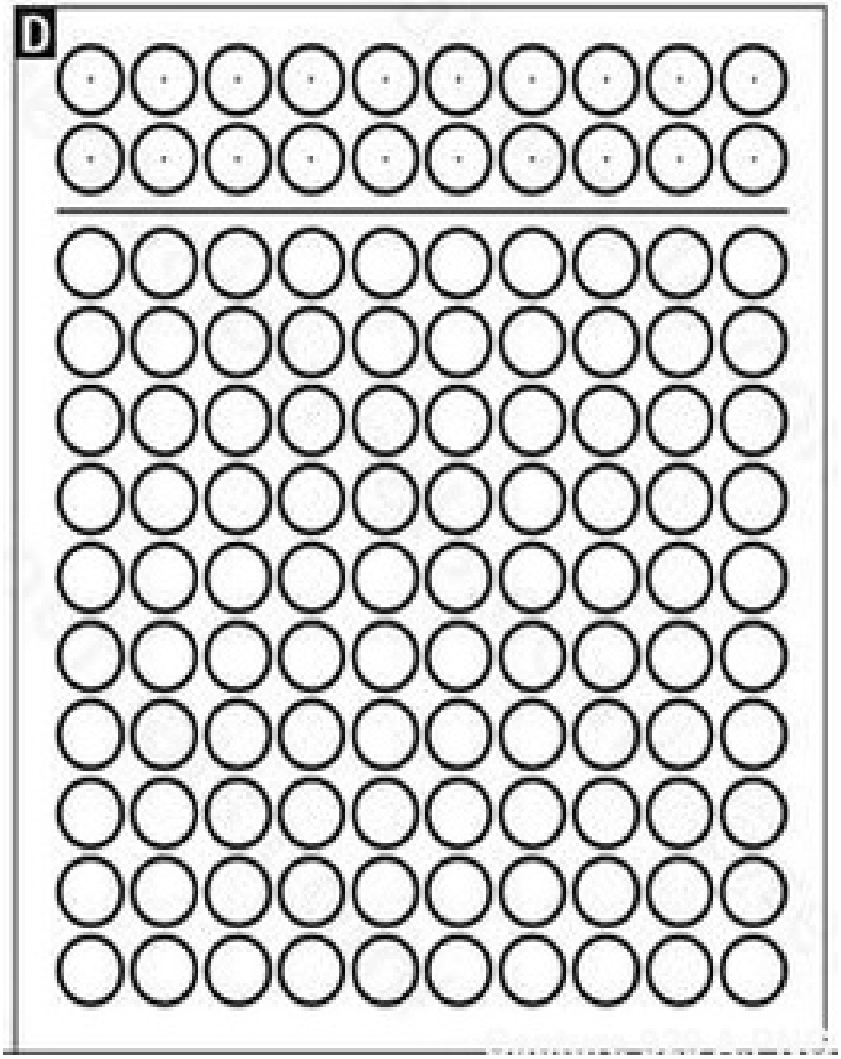


Figure 17. Number connection test B (NCT-B).

In the above test, results obtained are highly reliable and assuring results. In this battery of tests , a type of score called as Psychometric Heptaic Score-PHES is used to assess the parameters like visuoconstructive capabilities(12,44) attention and perception of vision. These tests are easily applicable and where found out to be highly specific for diagnosing hepatic encephalopathy in these patients .

Digit Symbol Test

Main disadvantage of these tests is that various confounding factors are there and the necessity for their normalization and from among the general population is required . At present, normalized values are available only in few European countries like Britain, Spain, Italy and Germany.



Serial Dotting Test

There are few Psychometric tests based on Computers provide us an accurate method of estimating the reaction times and hence yield us more precise assessment .. Other devices include Scan test which is based on the Sternberg paradigm is helpful in assessing those alterations in the cognitive functions and also to detect subtle defects in the memory as well as attention .

Tests to assess Neurophysiology

Electroencephalography (EEG *)*

The EEG is an investigation which is used to assess the neuronal activity of the cerebral cortex .In these patients, with hepatic encephalopathy the following findings are noticed.

1) A progressive slowing of the normal Alpha Wave frequency
2) Theta wave shows bursts of slower activity to begin with seen in the temporal areas, subsequently seen over the entire scalp
3) Later , further slowing is noticed in the Delta wave may then occur.
4) Arrhythmic Delta Triphasic activity occur in patients with higher grades .
5) In coma there occurs slower and delta activity with lower voltage

- However, the above findings as noticed in the following conditions which can be clinically differentiated include encephalopathies due to metabolic causes like hyponatraemia, uraemia
- Drug - induced encephalopathies with the drugs like Valproate, Baclofen and Lithium

There is a varied sensitivity for diagnosing Hepatic Encephalopathy. The abnormal EEG is noted in 43% to 100%patients of Overt Encephlopathy and in 8% to 40 %of patients with Cirrhosis and remaining clinically stable

Evoked potentials

On the stimulation of somatosensory nerves carrying auditory, visual functions there occurs a generation of potentials with the passive perception those sensory stimuli are called Exogenous Evoked Potentials.

Main advantage of this investigation is its ability to asses activities of both brainstem and cortical. With both minimal and overt hepatic encephalopathies, there occurs some abnormalities of EPs and they indicate the underlying deranged cortical function but still the results obtained are not so consistent as they require to be normalized .

Endogenous or cognitive EPs *:*

They are evoked by some activity of cognitive functions .A best type of this type namely P300 is evoked on the perception of either an infrequently delivered auditory and visual stimulus interspersed in a continuum of otherwise non relevant and recurrent stimuli.

The evaluation with P300 latency helps greatly in detecting the MHE and for following up. Thus it has a greater diagnostic value compared to the other tests. It cannot be used in higher grades of encephalopathy as the technique and method of this test requires the cooperation from the patient .

Critical flicker fusion frequency (55, 56, 57)

Critical Flicker Fusion Frequency (CFF) is a method in which the ability to perceive a flickering of light or otherwise a fused light with the alterations in its frequency is utilized .

It has been detected that 39 Hz is the cut off frequency in delineating those patients with Overt encephalopathy from those with stable patients and also delineating minimal hepatic encephalopathy from those cirrhosis yet

INSTRUMENT FOR MEASURING CFF

HEPATONORM ANALYZER

Figure 1: Examination hepatonorm

clinically stable patients. The sensitivity and specificity of CFF has been reported as 55% percentage and 100% respectively.

Several authors have validated the use of Critical Flicker Frequency in detecting and further follow up of patients with Minimal Hepatic Encephalopathy (68, 69, 70) .

Smooth pursuit eye movements (58)

They are the conjugate movements of the eye by which the eye pursues the moving objects and their recordings in patients with minimal

hepatic encephalopathy reveal smooth pursuit movements are affected while in patients with overt hepatic encephalopathy those movements are either significantly affected or totally lost .These defects indicate the underlying clinical condition of the patient and alterations in the psychometric functions for further monitoring .

Functional and Structural Cerebral imaging

Various Radiological investigations are available as non invasive investigations for the imaging of cerebral structures and its metabolism .

Cerebral CT and MR imaging

1) With routine cerebral CT and MR imaging there occurs atrophy of cerebrum and cerebellum which does not necessarily correlate with those impairments in Neuropsychological functions (59,60) .

Furthermore, cerebral atrophy is not a characteristic abnormality of hepatic encephalopathy .

2) On MRI T 1 - weighted images, hyperintensity in the Globus Pallidus of basal ganglia is noticed (60) . It does not correlate with the grades of the underlying hepatic encephalopathy.

Manganese has been implicated for the hyperintensities of basal ganglia and also features of Parkinsonism . The concentrations of Manganese is raised due to liver failure and the portosystemic shunting of prolonged duration. Routine CT and MRI of Cerebral imaging does not have diagnostic significance in these patients.

Newer and currently improved techniques of MRI are more helpful like Magnetization transfer and diffusion - weighted imaging assess the water content and its distribution in the Cerebrum. Haemodynamic responses related to the brain is assessed with the help of Functional MRI .With the utilization of Volumetric MRI , as the name implies , volumes of either as a whole brain or focused at a specific area of the brain able to measure precisely and can monitor even a little difference in the size of the brain .

Cerebral MRS

Currently , Proton magnetic resonance spectroscopy is used to assess various brain metabolites of significance like myoinositol , glutamate, glutamine having their roles in the development of hepatic encephalopathy. After getting released in the metabolism of Ammonia in

the Astrocytes the concentration of glutamine is increased in the Cerebrospinal fluid and Cerebral tissues , and tends to parallel the stages of hepatic encephalopathy .

There occurs a reduction in the brain content of myoinositol detected by Magnetic Resonance Spectroscopy as a result of raised intracellular osmolality caused by the increased concentration of glutamine and as a compensation .This type of characteristic changes also follows parallel to the severity of impairment of neropsychiatric functions .

Also it is noticed that a relative decrease in the myoinositol and choline resonances along with a relative increase in the composite glutamine/ glutamate resonance indicate changes in astrocyte volume homeostasis.

Levels of Ammonia in the Blood

When a patient is not presenting as a known case of Cirrhosis along with fluctuating sensorium and neurological features ,estimation of blood ammonia will greatly help in the differential diagnosis of hepatic encephalopathy as they may not have deranged LFT with minimal or no symptoms .

MATERIALS AND METHODS

PLACE OF STUDY:

This study has been carried out at the General Medicine OP and wards, Department of MGE OP and wards at Govt. Stanley hospital, Chennai.

STUDY PERIOD:

Six months (From June2013 to November 2013).

STUDY DESIGN:

This is a Prospective Observational Study.

ETHICAL COMMITTEE APPROVAL:

The ethical committee approval was obtained for this study.

PATIENT SELECTION:

INCLUSION CRITERIA:

1)Age more than 18 years and below 70 years

2)All patients who have been diagnosed as cirrhosis of the liver and detected by clinical, serological, biochemical, assessments and USG.

EXCLUSION CRITERIA:

1. Patients aged below 18 years and above 70 years.

2. Patients with overt hepatic encephalopathy had variceal bleed within 6 weeks.

3. Patients diagnosed as Hepatocellular Carcinoma

4. Patients who had undergone TIPS or shunt surgery.

5. Patients who had taken alcohol in last 6 weeks.

6. Known Patients with cognitive impairment disorders as Alzhiemers disease, Parkinsonism.

7. Patients who are already taking sedatives, antidepressants.

8. Patients with impairment of vision .

METHODOLOGY

100 Patients who has been diagnosed as cirrhosis based on clinical, biochemical, serological and ultrasonogram visiting in Medicine OP, MGE OP and admitted in Medical wards and MGE wards and 50 normal people as control group from June 2013 to November 2013 are included in the study. Patients will be subjected to symptom analysis, clinical examination, laboratory investigations, Psychometric tests and Critical Flicker Frequency test to establish the current degree of encephalopathy. The final analysis was made at the end of the study to achieve the aforementioned goals.

DISCUSSION

This study includes 150 patients with 100 people as proven cases of Cirrhosis and 50 people as controls for the Psychometric tests . All the patients under the study were found to have no neurological disorder or psychiatric illness .

SEX	CASES	PERCENTAGE	CONTROLS	PERCENTAGE
MALE	76	76 %	32	64 %
FEMALE	24	24 %	18	36 %
TOTAL	100		50	

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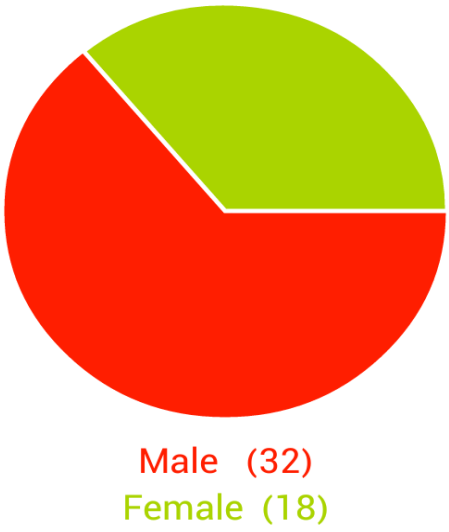
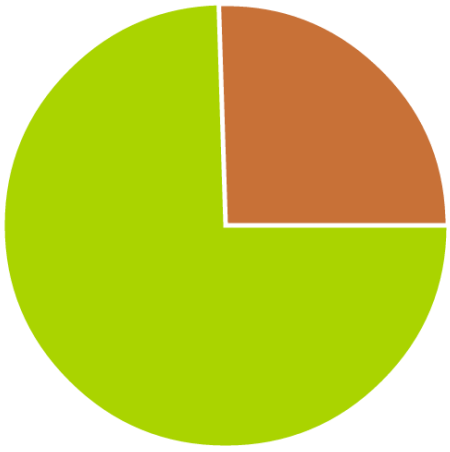


CONTROLS



CASES

There were 76 males and 24 females in the study group .There were 32 males and 18 females in the control group . In both the grops , the predominance of males is seen .

	Group	N	Mean	Std. Deviation
Age in years	Control	50	40.38	11.820
	Study	100	41.03	12.333

Mean age of presentation is 40 years with the youngest being 19 years and oldest as 69 years .The mean age of study group is 41 yrs and of controls is 40 years .

Alcoholic

INTAKE OF ALCOHOL	Frequency	Percent
Yes	59	59.0
No	41	41.0
Total	100	100.0

In the study group , only males are consuming alcohol with no females consume alcohol . There are 59 males who are alcoholic among the total of 76 males (77 %)

Viral markers

	Frequency	Percent
Negative	30	30.0
HBV +	62	62.0
HCV +	7	7.0
Wilson’s	1	1.0
Total	100	100.0

There were 62 patients with Hepatitis B virus positive cases ,7 as Hepatitis C positivity with only one case of proven case of Wilson’s disease .

Bilirubin level

Bilirubin (mg/dl)	**Frequency**	**Percent**
1-2	**28**	**28.0**
2-3	32	32.0
> 3	40	40.0
Total	100	100.0

There were 40 patients with Bilirubin level more than 3 mg/dl , 32 cases between 2-3 mg/dl and the rest 28 cases with less than 2 mg/dl .

Serum Albumin

ALBUMIN (mg/dl)	Frequency	Percent
> 3.5	23	23.0
2.5-3.5	42	42.0
< 2.5	35	35.0
Total	100	100.0

There were 42 patients with albumin level between 2.5 to 3.5 mg/dl , 35 patients with less than 2.5 mg/dl and the remaining 23 patients with more than 3.5 mg/dl .

Ascites

ASCITES	Frequency	Percent
Absent	39	39.0
Moderate	30	30.0
Severe	31	31.0
Total	100	100.0

Ascites was severe in 31 patients, moderate in 30 patients and no ascites in 39 patients .

PROTHROMBIN TIME

PT PRLONGATION (SEC)	Frequency	Percent
1-4	41	41.0
5-6	32	32.0
> 6	27	27.0
Total	100	100.0

There was a prolongation of Prothrombin time when compared to the control with more than 1 to 4 seconds in 41 patients , more than 5 to 6 seconds in 32 patients and more than 6 seconds in 27 patients .

CHILD PUGH'S CLASS

CPT CLASS	Frequency	Percent
5-6	29	29.0
7-9	40	40.0
10-15	31	31.0
TOTAL	100	100.0

There were 29 patients in CPT Class A, 40 patients in Class B and 31 patients in Class C .

PSYCHOMETRIC TESTS

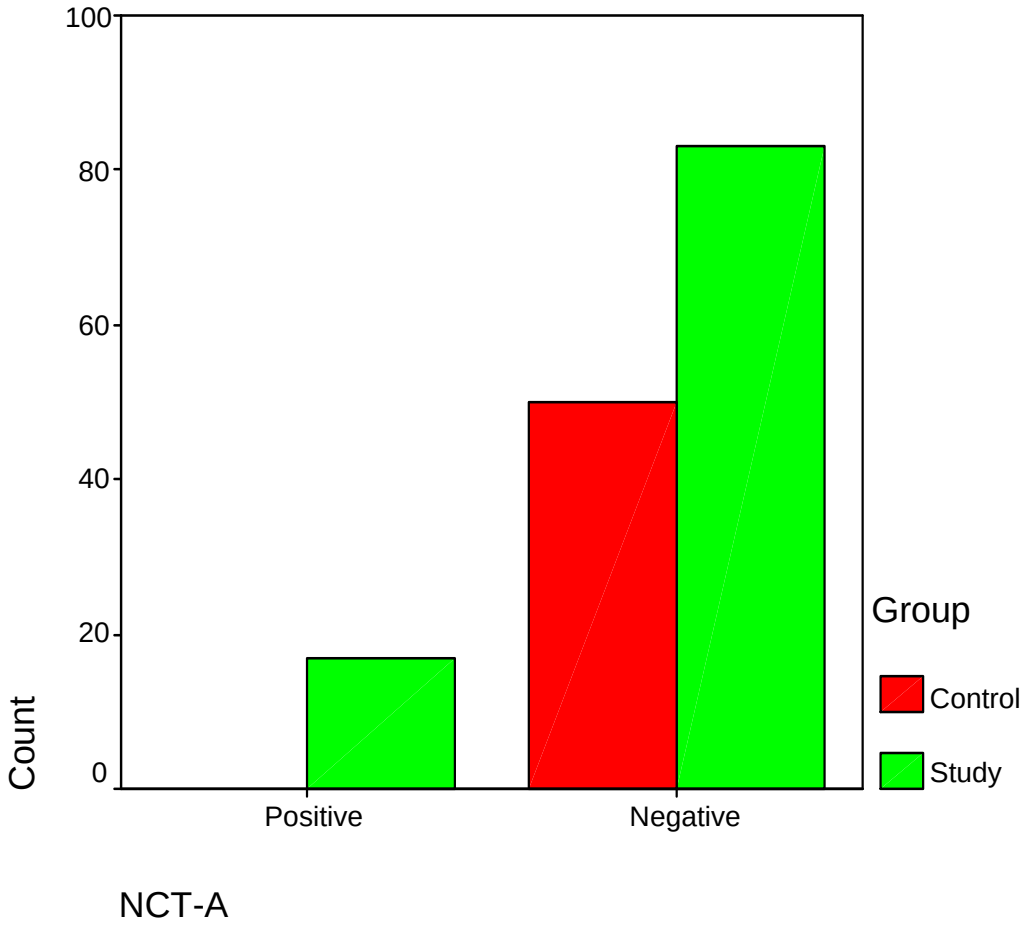
	Group	N	Mean	Std. Deviation
NCT-A	Control	50	57.38	9.243
	Study	100	85.81	31.746
NCT-B	Control	50	152.34	19.448
	Study	100	224.07	55.332
DST	Control	50	194.46	34.929
	Study	100	270.38	49.218
LTT	Control	50	575.60	38.255
	Study	100	662.62	62.555
SDT	Control	50	207.40	96.533
	Study	100	271.28	76.997
CFF (Hz)	Control	50	47.882	4.6541
	Study	100	36.866	3.7761
CFF(SD)	Control	50	1.5770	.74642
	Study	100	1.2390	.70188

There exist significant differences in the performance of all the Psychometric tests as indicated by the values of median , and standard deviation when compared between the study and the control groups .(p=0.000)

NCT-A * Group

			Group		
			Control	Study	Total
NCT-A	Positive	Count	0	17	17
		% within NCT-A	.0%	100.0%	100.0%
		% within Group	.0%	17.0%	11.3%
	Negative	Count	50	83	133
		% within NCT-A	37.6%	62.4%	100.0%
		% within Group	100.0%	83.0%	88.7%
Total		Count	50	100	150
		% within NCT-A	33.3%	66.7%	100.0%
		% within Group	100.0%	100.0%	100.0%

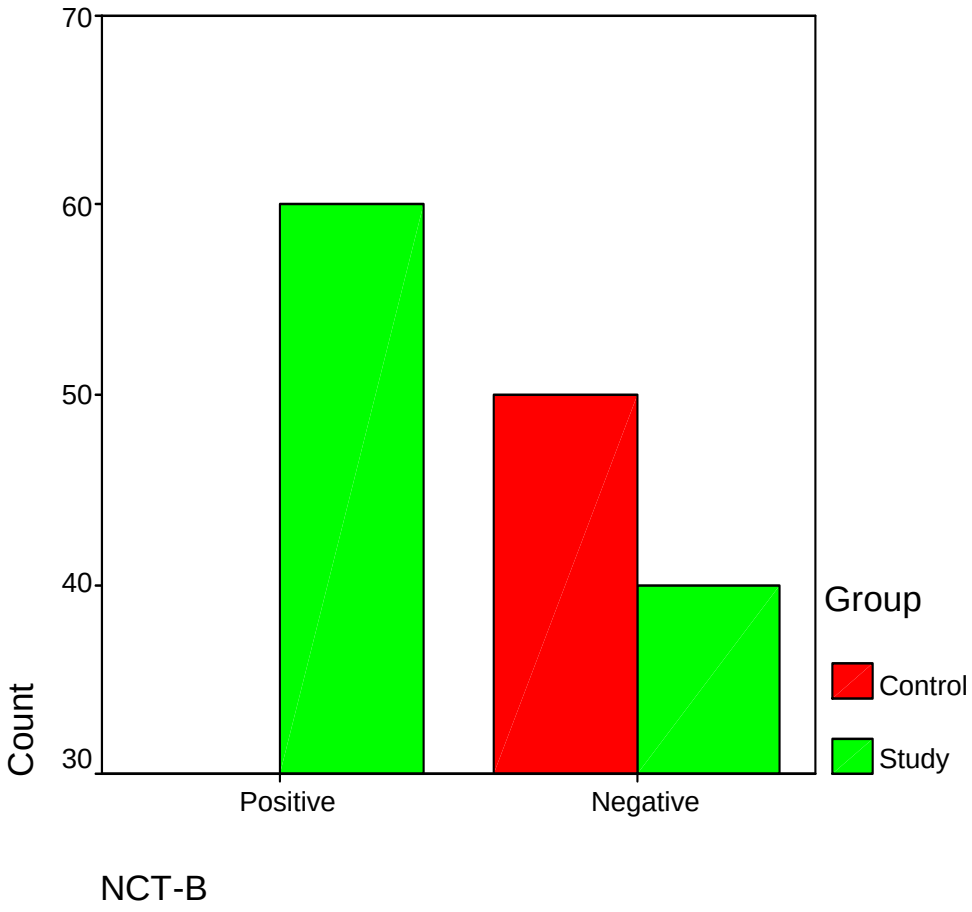
Number Connection Test –A was positive in only study group with no positivity at all in the control group .



NCT-A Test turned out to be positive in only study group .

			Group		
			Control	Study	Total
NCT-B	Positive	Count	0	60	60
		% within NCT-B	.0%	100.0%	100.0%
		% within Group	.0%	60.0%	40.0%
	Negative	Count	50	40	90
		% within NCT-B	55.6%	44.4%	100.0%
		% within Group	100.0%	40.0%	60.0%
Total		Count	50	100	150
		% within NCT-B	33.3%	66.7%	100.0%
		% within Group	100.0%	100.0%	100.0%

Number Connection Test –B is positive in 60 patients in the study group only .

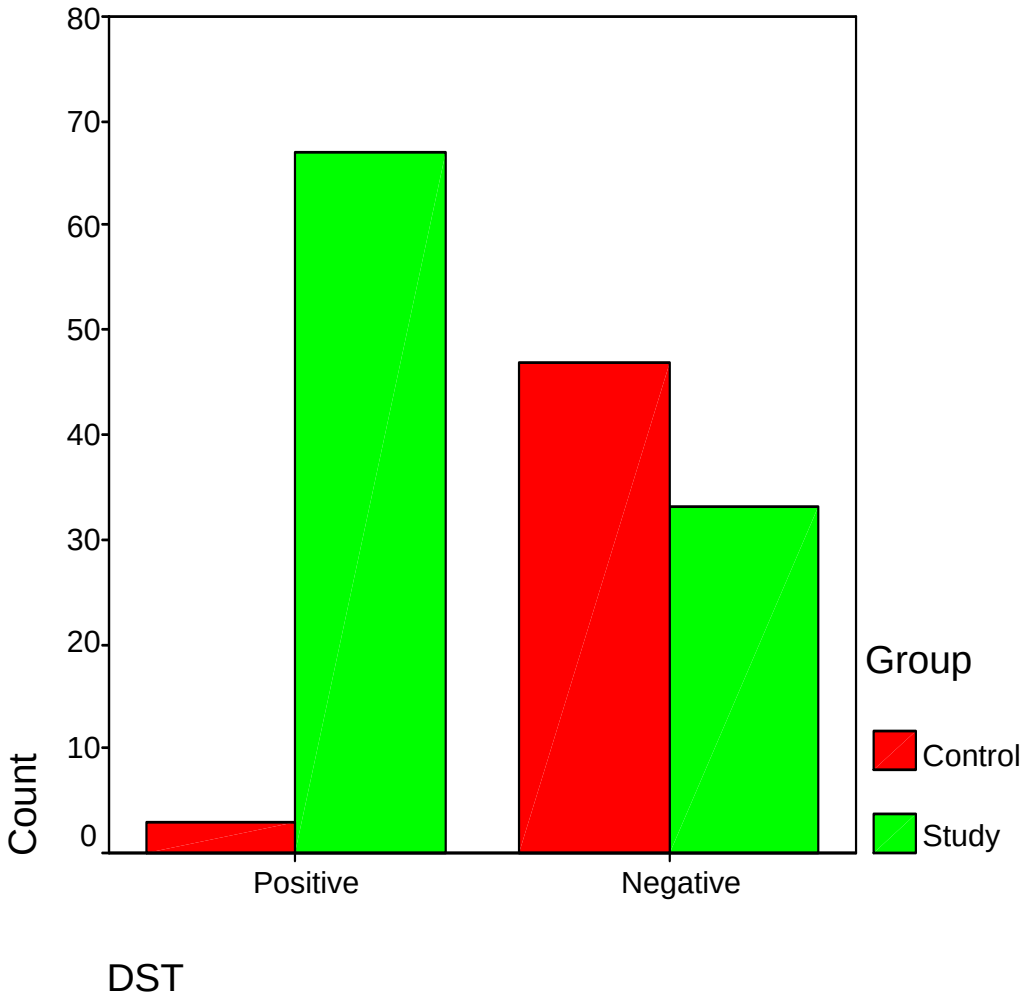


NCT –B was positivity in the study group only.

DIGIT SYMBOL TEST

			Group		
			Control	Study	Total
DST	Positive	Count	3	67	70
		% within DST	4.3%	95.7%	100.0%
		% within Group	6.0%	67.0%	46.7%
	Negative	Count	47	33	80
		% within DST	58.8%	41.3%	100.0%
		% within Group	94.0%	33.0%	53.3%
Total		Count	50	100	150
		% within DST	33.3%	66.7%	100.0%
		% within Group	100.0%	100.0%	100.0%

There was totally 70 patients showed positivity for Digit SymbolTest among which 67 people (95.7 %)were from the study group with the remaining 3 people (4.3%) from the control group.

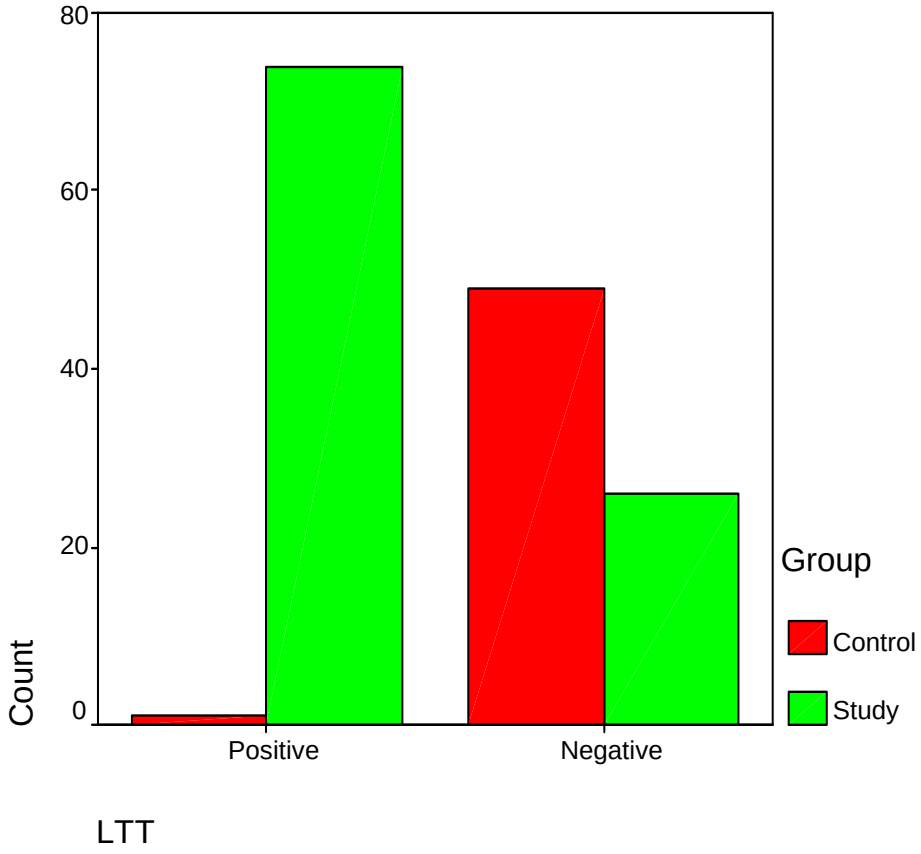


Predominantly, there were more positive people from the study group .

LINE TRACING TEST (LTT)

			Group		
			Control	Study	Total
LTT	Positive	Count	1	74	75
		% within LTT	1.3%	98.7%	100.0%
		% within Group	2.0%	74.0%	50.0%
	Negative	Count	49	26	75
		% within LTT	65.3%	34.7%	100.0%
		% within Group	98.0%	26.0%	50.0%
Total		Count	50	100	150
		% within LTT	33.3%	66.7%	100.0%
		% within Group	100.0%	100.0%	100.0%

Totally 75 patients were positive for LTT out of which 74 (98.7%) people were from the study group.



Almost, Line tracing test was positive in the study group leaving a fraction of positivity to the control group .

SERIAL DOTTING TEST (S D T)

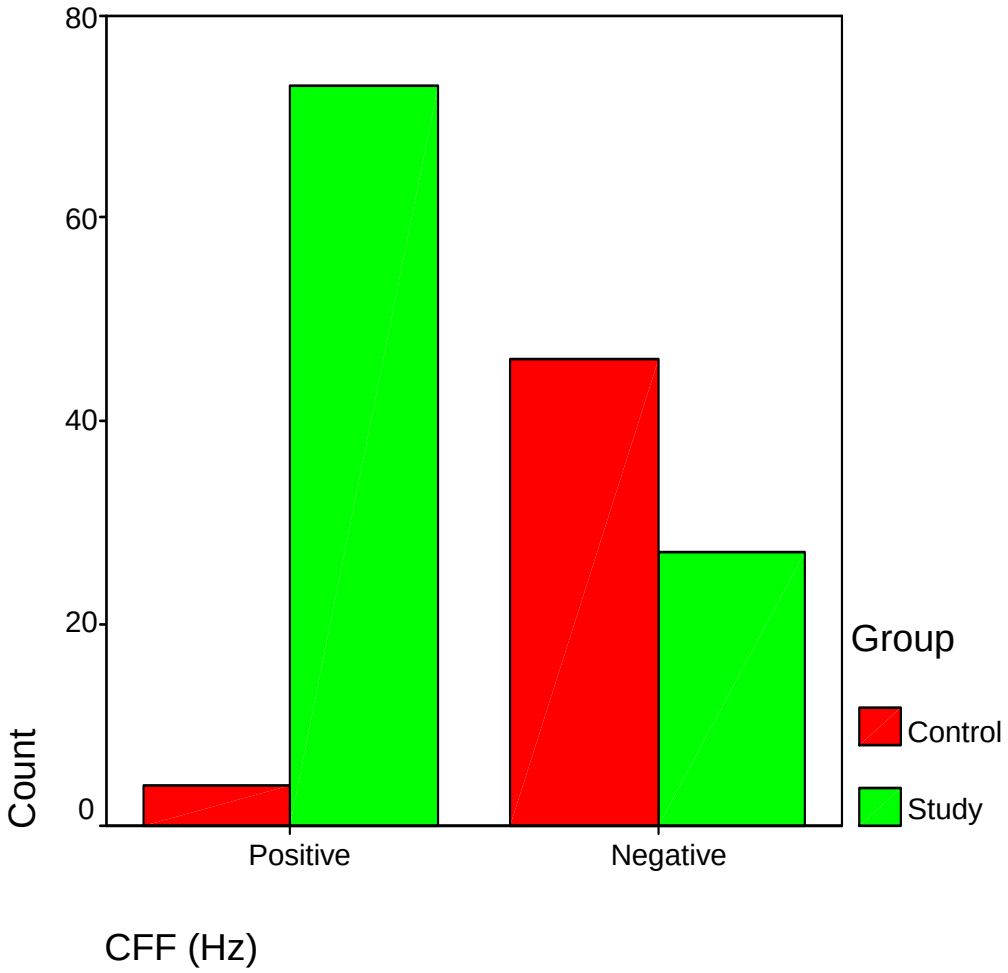
			Group		
			Control	Study	Total
SDT	Positive	Count	3	70	73
		% within LTT	4.1%	95.9%	100.0%
		% within Group	6.0%	64.0%	48.7%
	Negative	Count	47	30	77
		% within LTT	61.1%	38.9%	100.0%
		% within Group	94.0%	30%	51.3%
Total		Count	50	100	150
		% within LTT	33.3%	66.7%	100.0%
		% within Group	100.0%	100.0%	100.0%

There were totally 73 people showed positivity for Serial Dotting Test out of which 70 people (95.9%) were from the study group while the remaining 3 people (4.1%) were from the control group.

CRITICAL FLICKER FREQUENCY (CFF)

			Group		
			Control	Study	Total
CFF (Hz)	Positive (<39Hz)	Count	4	73	77
		% within CFF (Hz)	5.2%	94.8%	100.0%
		% within Group	8.0%	73.0%	51.3%
	Negative (>39Hz)	Count	46	27	73
		% within CFF (Hz)	63.0%	37.0%	100.0%
		% within Group	92.0%	27.0%	48.7%
Total		Count	50	100	150
		% within CFF (Hz)	33.3%	66.7%	100.0%
		% within Group	100.0%	100.0%	100.0%

There were 73 patients (94.8%) who turned out to be positive among the study group and 4 patients (5.2%)from the control group were positive in Critical Flicker Frequency Test . (p value =0.000)



Critical Flicker Frequency Test was more positive in the study group than the control group. Only a few positivity is noted among the control group.

SUMMARY

- In our study , 100 patients who have been diagnosed and proven as a case of cirrhosis were include under the study group and 50 other people were included as control group without any evidence of liver disease .Before the study was commenced , all the people in both group were clinically examined and were ruled out of any neuropsychological abnormalities .We utilized the Psychometric tests in the study group and compared with the age , sex and education wise matched .In addition ,Critical Flicker Frequency Test was carried out in both the study group and the results were compared for further analysis .

- In our study, there was a preponderance of males in both the study groups with 76 males in the study group comprising 76% and 32 males in the control group as 64% of the members in their groups .

- Mean age of presentation is 40 years with the youngest being 19years and oldest as 69 years .The mean age of the study group is 41 yrs while that of the controls is 40 years .

- Regarding the consumption of alcohol, in the study group , only males are consuming alcohol with totally no females consume alcohol . There are 59 males who are alcoholic among the total of 76 males (77 %) in the study group.

- Among the 100 patients in the study group Hepatitis B virus is the causative agent of cirrhosis in 62 patients comprising majority of the study group with 62% while 7 patients have been affected by Hepatitis C virus constituting only 7% and with only one case of Wilson's disease (1%) .In the remaining, Alcohol is the main causative factor constituting 30% in the study group .

- In our study, 40 patients had Bilirubin values more than 3 mg/dl while 32 patients with values between 2 to 3 mg/dl.

- Albumin levels in the patients of between 2.5 to 3.5 mg/dl were 42 in number (42%) while 35 patients had low levels of Albumin of less than 2.5 mg/dl.

- Ascites was moderate in 30 patients and severe in 31 patients while 39 people were free of ascites at the time of the study.

- Prothrombin time was prolonge compared to the control value by 6seconds in 27 patients and by 5 to 6 seconds in 32 patients .

- Majority of the patients in our study fell under Child Pugh's Classes B as 40 patients and 31 patients under Class C.

- Performances of the Psychometric tests among the study group and the control group yielded significant results among the study group . (p=0.000)

- Critical Flicker Frequency Test was more positive in the study group then the control group and was found to be statistically significant values obtained as 0.000 indicating the higher significance when compared with the controls.

- Both the Psychometric tests and Critical Flicker Frequency Test were useful in detecting cases of Minimal Hepatic Encephalopathy.

- Critical Flicker Frequency Test was found to be more positive among the study group with 73% than the control group and hence the ability to detect the cases of Minimal hepatic encephalopathy than the Psychometric tests.

CONCLUSION

Our study demonstrated the occurrence of Minimal Hepatic Encephalopathy (MHE) in patients with Cirrhosis irrespective of the etiology even in the presence of stable clinical condition . Both Critical Flicker Frequency (CFF) Test and Psychometric tests have been found out to be effective in detecting MHE . Psychometric tests have subjective variations due to their age factor , differences in education while CFF Test has no such limitations and more of objective in nature not requiring any educational qualification for undergoing and interpretation of the light stimulus and is reproducible .The detection of MHE in more numbers in our study may be due to higher number of patients with higher classes of Child Pugh classification .The presence of majority of the patients with Hepatitis B infection is due to our place of study being a tertiary care and a prestigious institute of Gastroenterology .

Hence, we would like to recommend the utilization of Critical Flicker Frequency (CFF) Test as an Out Patient Department based screening procedure and also for the monitoring of patients with cirrhosis yet with a stable clinical condition so as to detect MHE earlier and promptly institute the therapy to avoid the complications .

BIBILIOGRAPHY

1. Weissenborn K. Diagnosis of encephalopathy. Digestion 1998; **59** (Suppl. 2): 22 – 24 .
2. Ferenci P, Lockwood A, Mullen K et al. Hepatic Encephalopathy – definition, nomenclature, diagnosis, and quantification: Final report of the working party at the11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology 2002; **35**: 716 – 721.
3. Montagnese S, Middleton B, Skene D et al. Night – time Sleep disturbance does not correlate with neuropsychiatric impairment in patients with cirrhosis . Liver Int. 2009; **29**: 1372 – 1382.
4. Challenger F, Walshe JM. Methyl mercaptan in relation to foetor hepaticus . Biochem. *J.* 1955; **59**: 372 – 375.
5. Victor M, Adams RD, Cole M. The acquired (non Wilsonian) type of chronic hepatocerebral degeneration. *Medicine* 1965; **44**: 345 – 396.
6. Krieger S, Jauss M, Jansen O et al. Neuropsychiatric profile and hyperintense globus pallidus on T1 - weighted magnetic resonance images in liver cirrhosis . Gastroenterology 1996; **111** : 147 – 155 .
7. Cadranel JF , Lebiez E , DiMartino V et al. Focal neurological Signs in hepatic encephalopathy in cirrhotic patients: An underestimated entity? Am. J. Gastroenterol. 2001; **96**: 515 – 518.
8. Joebges EM , Heidemann M , Schimke N et al. Bradykinesia in minimal hepatic encephalopathy is due to disturbances in movement initiation . J. Hepatol. 2003; **38**: 273 – 280.
9. Miyata Y, Motomura S , Tsuji Y et al. Hepatic encephalopathy and reversible cortical blindness . Am. J. Gastroenterol. 1988; **83**: 780 – 782.

10. Averbuch - Heller L , Meiner Z . Reversible periodic alternating gaze deviation in hepatic encephalopathy . Neurology 1995; **45**: 191 – 192.
11. Gilberstadt SJ , Gilberstadt H , Zieve L et al. Psychomotor Performance defects in cirrhotic patients without overt encephalopathy . Arch. Intern. Med. 1980 **140**: 519 – 521.
12. Schomerus H , Hamster W . Neuropsychological aspects of Portal – systemic encephalopathy. Metab. Brain. *Dis.*1998; **13**: 361 – 377.
13. Parsons - Smith BG , Summerskill WHJ , Dawson AM et al. The electroencephalograph in liver disease. Lancet 1957.
14. Van der Rijt CC , Schalm SW , De Groot GH et al. Objective measurement of hepatic encephalopathy by means of automated EEG analysis . Electroencephalogr. Clin. Neurophysiol. 1984; **7**: 423 – 426.
15. Chu NS , Yang SS , Liaw YF . Evoked potentials in liver diseases . J. Gastroenterol. Hepatol. 1997; **12** : S288 – S29.
16. Amodio P , Del Piccolo F , Petten ò E et al. Prevalence and prognostic value of quantified electroencephalogram (EEG) alterations in cirrhotic patients. J. Hepatol. 2001; **35**: 37 – 45.
17. Montagnese S , Jackson C , Morgan MY . Spatio - temporal decomposition of the electroencephalogram in patients with cirrhosis . J. Hepatol. 2007; **46** : 447 – 458 .
18. Taylor - Robinson SD , Sargentoni J , Mallalieu RJ et al. Cerebral phosphorus - 31 magnetic resonance spectroscopy in patients with chronic hepatic encephalopathy. Hepatology 1994; **20** : 1173 – 1178 .

19. Taylor - Robinson SD, Sargentoni J , Marcus CD et al. Regional variations in cerebral proton spectroscopy in patients with chronic hepatic encephalopathy . Metab. *Brain Dis.* 1994 ; **9** : 347 – 359 .
20. O' Carroll RE , Hayes PC , Ebmeier KP et al. Regional cerebral blood flow and cognitive function in patients with chronic liver disease . Lancet 1991; **337** : 1250 – 1253 .
21. Lockwood AH , Murphy BW , Donnelly KZ et al. Positron - emission tomographic localization of abnormalities of brain metabolism in patients with minimal hepatic encephalopathy. *Hepatology* 1993; **18** : 1061 – 1068 .
22. Häussinger D , Kircheis G , Fischer R et al. Hepatic encephalopathy in chronic liver disease: A clinical manifestation of astrocyte swelling and low - grade cerebral edema? J.*Hepatol.* 2000; **32** : 1035 – 1038 .
23. Batki G , Fisch HU , Karlaganis G *et al.* Mechanism of the selective response of cirrhotics to benzodiazepines. Model experiments with triazolam . Hepatology 1987; **7**: 629 – 638.
24. Bajaj JS , Schubert CM , Heuman DM et al. Persistence of cognitive impairment after resolution of overt hepatic encephalopathy. Gastroenterology 2010; **138**: 2332 – 2340.
25. Conn HO, R ö ssle M , Levy L et al. Portosystemic myelopathy: spastic paraparesis after portosystemic shunting. Scand. J. Gastroenterol. 2006; **4**: 619 – 62.
26. Pinarbasi B, Kaymakoglu S, Matur Z et al. Are acquired hepatocerebral degeneration and hepatic myelopathy reversible? J. Clin. Gastroenterol. 2009; **43**: 176 – 181 .
27. Rikkers L , Jenko P , Rudman D et al. Subclinical hepatic encephalopathy: Detection, prevalence, and relationship to nitrogen metabolism . Gastroenterology 1978; **75**: 462 – 469.

28. Groeneweg M , Quero JC , De Bruijn I et al. Subclinical hepatic encephalopathy impairs daily functioning. *Hepatology* 1998; **28** : 45 – 49 .
29. Schomerus H , Hamster W . Quality of life in cirrhotics with minimal hepatic encephalopathy . Metab. *Brain Dis.* 2001; **16**: 37 – 41.
30. Schomerus H , Hamster W , Blunck H et al. Latent portasystemic encephalopathy. I. Nature of cerebral functional defects and their effect on fitness to drive . Dig. Dis. Sci. 1981; **26**: 622 – 630.
31. Kircheis G , Knoche A , Hilger N et al. Hepatic encephalopathy and fi tness to drive . Gastroenterology 2009; **137** : 1706 – 1715.
32. Amodio P , Del Piccolo F , Marchetti P et al. Clinical features and survival of cirrhotic patients with subclinical cognitive alterations detected by the number connection test and computerized psychometric tests . Hepatology 1999 ; **29** : 1662 – 1667 .
33. Das A , Dhiman RK , Saraswat VA et al. Prevalence and natural history of subclinical hepatic encephalopathy in cirrhosis. J. Gastroenterol. Hepatol. 2001; **16** : 531 – 535 .
34. Saxena N , Bhatia M , Joshi YK et al. Auditory P300 event - related potentials and number connection test for evaluation of subclinical hepatic encephalopathy in patients with cirrhosis of the liver: A follow - up study . J. Gastroenterol. Hepatol. 2001 ; **16** : 322 – 327 .
35. Lockwood AH, Yap EW, Wong WH . Cerebral ammonia metabolism in patients with severe liver disease and minimal hepatic encephalopath . J.Cereb. Blood Flow Metab. 199; **11**: 337 – 341.

36. Szerb JC, Butterworth RF. Effect of ammonium ions on synaptic transmission in the mammalian central nervous system. Prog. Neurobiol. 1992; **39**: 135 – 153
37. Córdoba J, Alonso J, Rovira A et al. The development of low grade cerebral edema in cirrhosis is supported by the evolution of 1H - magnetic resonance abnormalities after liver transplantation. J. Hepatol. 2001; **35**: 598 – 604.
38. Kale RA, Gupta RK, Saraswat VA et al. Demonstration of interstitial Cerebral edema with diffusion tensor MR imaging in type C hepatic encephalopathy. Hepatology 2006; **43**: 698 – 70.
39. Häussinger D, Laubenberger J, vom Dahl S et al. Proton magnetic resonance spectroscopy on human brain myo -inositol in hypoosmolarity and hepatic encephalopathy. Gastroenterology 1994; **107**: 1475 – 1480. C hepatic encephalopathy. Hepatology 2006; **43**: 698 – 706.
40. Laubenberger J, H ä ussinger D, Bayer S et al. Proton magnetic resonance spectroscopy of the brain in symptomatic and asymptomatic patients with liver cirrhosis. Gastroenterology 1997; **112**: 610 – 616.
41. Bemeur C, Desjardins P, Butterworth RF. Evidence for Oxidative / nitrosative stress in the pathogenesis of hepatic encephalopathy. Metab. Brain Dis. 2010; **25**: 3 – 9 .42)
42. Song G, Dhodda VK, Blei AT et al. GeneChip analysis Shows altered mRNA expression of transcripts of neurotransmitter and signal transduction pathways in the cerebral cortex of portacaval shunted rats . J. Neurosci. Res.2002; **68** : 730 – 737 .
43. Zhou BG, Norenberg MD. Ammonia downregulates GLAST mRNA glutamate transporter in rat astrocyte cultures. Neurosci. Lett. 1999; **276** : 145 – 148 .

44. Chan H , Zwingmann C , Pannunzio M et al. Effects of ammonia on high affi nity glutamate uptake and glutamate transporter EAAT3 expression in cultured rat cerebellar granule cells . Neurochem. Int. 2003 ; **43** : 137 – 146
45. Córdoba J , Sanpedro F , Alonso J , Rovira A. 1H magnetic resonance in the study of hepatic encephalopathy in humans . Metab. Brain Dis. 2002; **17** : 415 - 429 .
46. Barbaro G , Di Lorenzo G , Soldini M et al. Flumazenil for hepatic encephalopathy grade III and IVa in patients with cirrhosis: an Italian multicentre double - blind, placebo - controlled, cross - over study . Hepatology 1998; **28** : 374 – 378
47. Mousseau DD , Baker GB , Butterworth RF . Increased density of catalytic sites and expression of brain monoamine oxidase A in humans with hepatic encephalopathy. J. Neurochem. 1997; **68**: 1200 – 1208.
48. Bergeron M, Reader TA , Layrargues GP et al. Monoamines an metabolites in autopsied brain tissue from cirrhoticpatients with hepatic encephalopathy . Neurochem. Res. 1989; **14** : 853 – 859 .
49. Butterworth RF . Alterations of [3H]8 - OH – DPAT and [3H]ketanserin binding sites in autopsied brain tissue from cirrhotic patients with hepatic encephalopathy .Neurosci. Lett. 1994 ; **182** : 69 – 72 50)
50. Vorobioff J, Garcia- Tsao G , Groszmann R et al. Long- term haemodynamic effects of ketanserin, a 5 – hydroxytryptamine blocker, in portal hypertensive patients . Hepatology 1989; **9**:88 – 91.
51. Rao VL , Gigu è re JF , Layrargues GP et al. Increased activities of MAOA and MAOB in autopsied brain tissue from cirrhotic

patients with hepatic encephalopathy . Brain Res. 1993 ; **621** : 349 – 352

52. Mousseau DD, Perney P, Layrargues GP et al. Selective loss of pallidal dopamine D2 receptor density in hepatic encephalopathy . Neurosci. Lett. 1993; **162**:192 – 196.
53. Rockey DC, Boyles JK, Gabbiani G et al. Rat hepatic lipocytes express smooth muscle actin upon activation in vivo and in culture .J.Submicrosc. Cytol. Pathol. 1992; **24**: 193 – 203.
54. Saab S, Tam SP, Tran BN et al. Myosin mediates contractile force generation by hepatic HSCs in response to endothelin - 1 . J. Biomed Sci. 2002; **9**: 607 – 612.
55. Kircheis G , Wettstein M , Timmermann L et al. Critical flicker frequency for quantifi cation of low - grade hepatic encephalopathy. *Hepatology* 2002; **35** : 357 – 366 .
56. Romero - G ó mez M, C ó rdoba J, Jover R et al. Value of the critical flicker frequency in patients with minimal hepatic encephalopathy. Hepatology 2007; **45** : 879 – 885 .
57. Sharma P, Sharma BC , Puri V et al. Critical flicker frequency: diagnostic tool for minimal hepatic encephalopathy. J. Hepatol. 2007; **47**: 67 – 73.
58. Montagnese S , Gordon HM , Jackson C et al. Disruption of smooth pursuit eye movements in cirrhosis: relationship to hepatic encephalopathy and its treatment . Hepatology 2005 ; **42** : 772 – 781.
59. Morgan MY. Cerebral magnetic resonance imaging in patients with chronic liver disease . Metab. Brain Dis. 1998; **13** : 273 – 290

60. Grover VPB, Dresner MA, Forton DM et al. Current and future applications of magnetic resonance imaging and spectroscopy of the brain in hepatic encephalopathy. World J. Gastroenterol. 2006; **12**: 2969 – 2978 .
61. Inoue E , Hori S , Narumi Y et al. Portal – systemic encephalopathy: presence of basal ganglia lesions with high signal intensity on MR images . Radiology 1991; **179** : 551 – 555.
62. Pujol A , Pujol J , Graus F et al. Hyperintense globus pallidus on T1 - weighted MRI in cirrhotic patients is associated with severity of liver failure . Neurology 1993; **43**: 65 – 69.
63. Thuluvath PJ , Edwin D , Yue NC et al. Increased signals seen in the globus pallidus in T1 - weighted magnetic resonance imaging in cirrhotics are not suggestive of chronic hepatic encephalopathy . Hepatology 1996; **24** : 282 – 283 .
64. Nolte W , Wiltfang J , Schindler C et al. Portosystemic hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in patients with cirrhosis: clinical, laboratory, psychometric and electroencephalographic investigations . Hepatology 1998; **28** : 1215 – 1225.
65. Rose C, Butterworth RF , Zayed J et al. Manganese deposition in basal ganglia structures results from both portal - systemic shunting and liver dysfunction . Gastroenterology 1999; **117** : 640 – 644 .
66. Jayakumar AR , Rama Rao KV , Kalaiselvi P et al. Combined of ammonia and manganese on astrocytesin cluture. Neurochem. *Res.* 2004; **29**: 2051 – 2056 .
67. Shawcross DL , Shabbir SS , Taylor NJ et al. Ammonia and neutrophil in the pathogenesis of hepatic encephalopathy in cirrhosis . Hepatology 2010; **51**: 1062 – 1069.

68. Ahboucha S , Butterworth RF . The neurosteroid system: Implication in the pathogenesis of hepatic encephalopathy. Neurochem. Int. 2008; **52**: 575 – 587 .
69. Journal of Clinical and Experimental Hepatology | March 2012 | Vol. 2 | Suppl 1 | S6–S396
70. Journal of Hepatology 47 (2007) 10–11 Critical Flicker Frequency for Diagnosis of Minimal Hepatic Encephalopathy in Patients with Cirrhosis C Sateesh Chandra, P Murali Krishna, LRS Girinadh Department of Gastroenterology, Andhra Medical College, Visakhapatnam
71. Journal of Hepatology 42 (2005) S45–S53- Minimal hepatic encephalopathy:diagnosis, clinical significance and recommendation Marı´a Ortiz1, Carlos Jacas, Juan Co´rdoba

PROFORMA

NAME :

SL. NO :

AGE / SEX :

OCCUPATION:

ADDRESS WITH CONTACT NUMBER:

IP NO:

DATE OF ADMISSION:

DATE OF DISCHARGE/ DEATH:

HISTORY:

H/O JAUNDICE

H/O MALENA

H/O HEMETEMESIS

H/O BLOOD TRANSFUSION

H/O ANY ENDOSCOPIC INTERVENTION

H/O BLEEDING FROM ANY OTHER SITES

H/O ALTERED SLEEP PATTERN

H/O ANY ALTERED SENSORIUM

H/O CONVULSION

H/O ALCOHOL INGESTION

Physical examination

Sensorium

Pallor

Icterus

Pedal edema

BP: PR:

CVS -

RS -

P/A -

CNS –FLAPS +/-

INVESTIGATIONS

CBC – TC

DC

ESR

HB

PLATELETS

BLOOD SUGAR

UREA

SERUM CREATININE

SODIUM

POTASSIUM

CHLORIDE

BICARBONATE

LFT- TOTAL BILIRUBIN
DIRECT BILIRUBIN
INDIRECT BILIRUBIN
SGOT
SGPT
SAP
TOTAL PROTEINS
ALBUMIN
PT
APTT
INR
VIRAL MARKERS
ULTRASONOGRAM OF ABDOMEN

URINE EXAMINATION
ECG

PSYCHOMETRIC TESTS

NUMBER CONNECTION TEST A-

NUMBER CONNECTION TEST B-

DIGIT SYMBOL TEST

LINE TRACING TEST

SERIAL DOT TEST

CRITICAL FLICKER FREQUENCY TEST

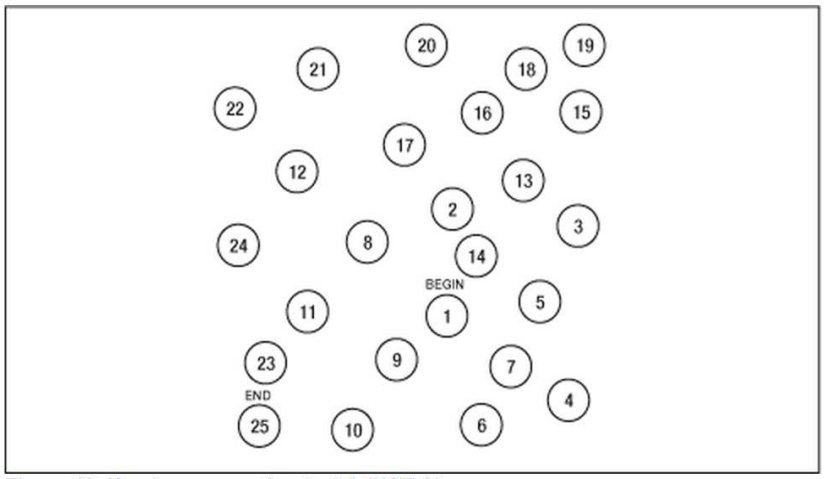


Figure 16. Number connection test A (NCT-A).

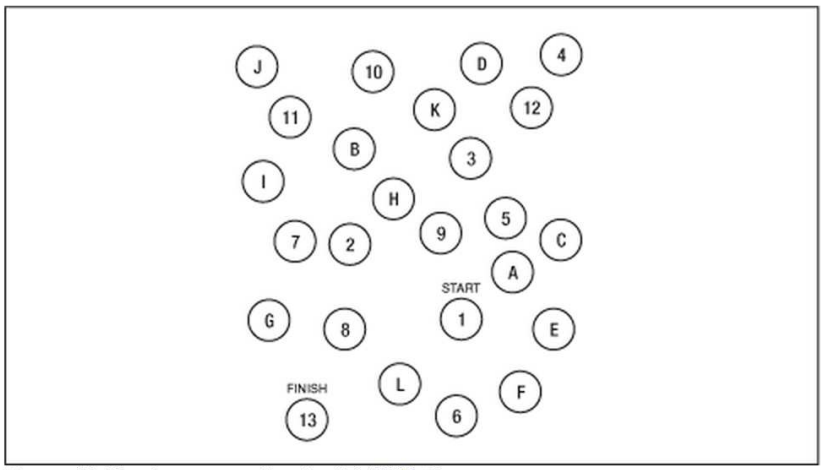


Figure 17. Number connection test B (NCT-B).

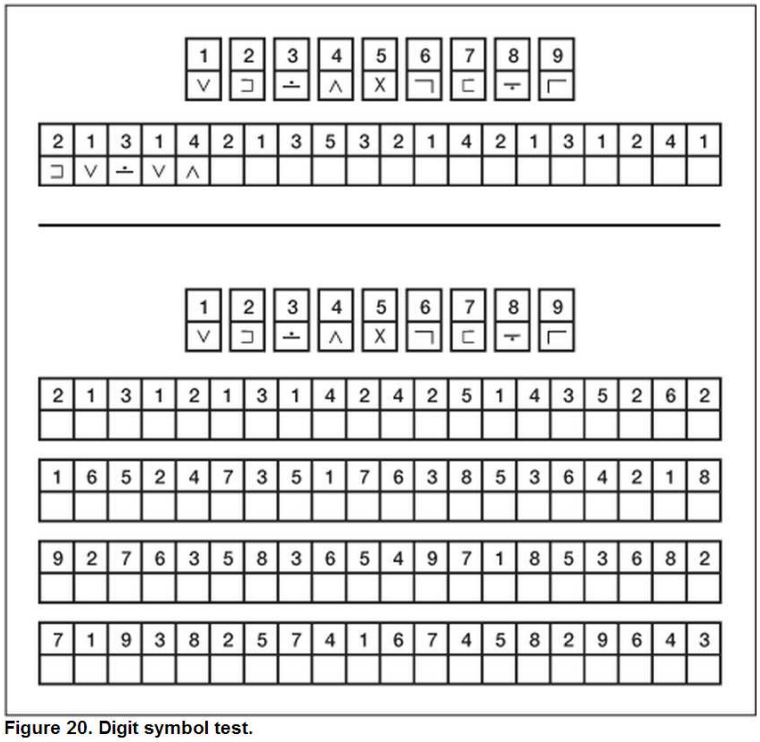
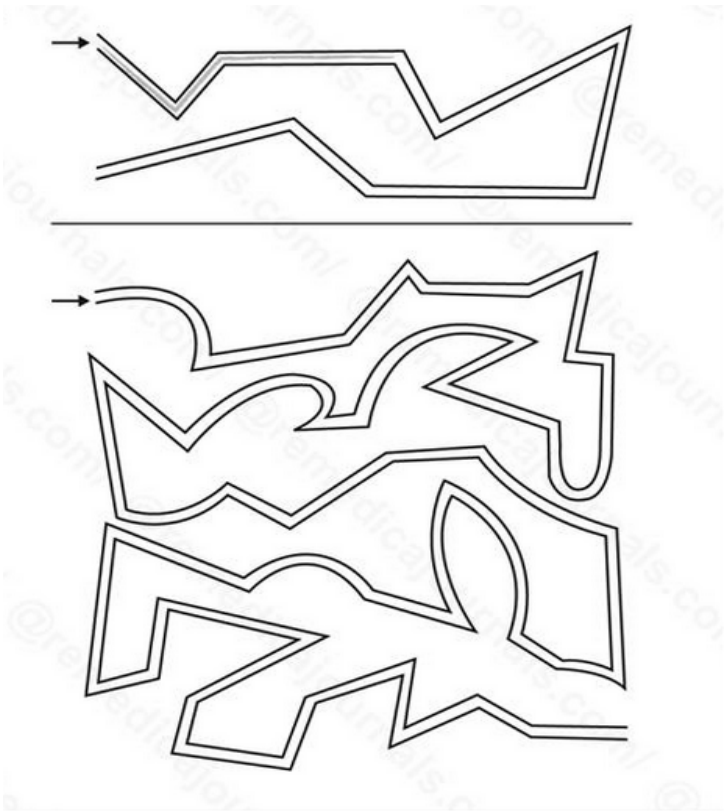
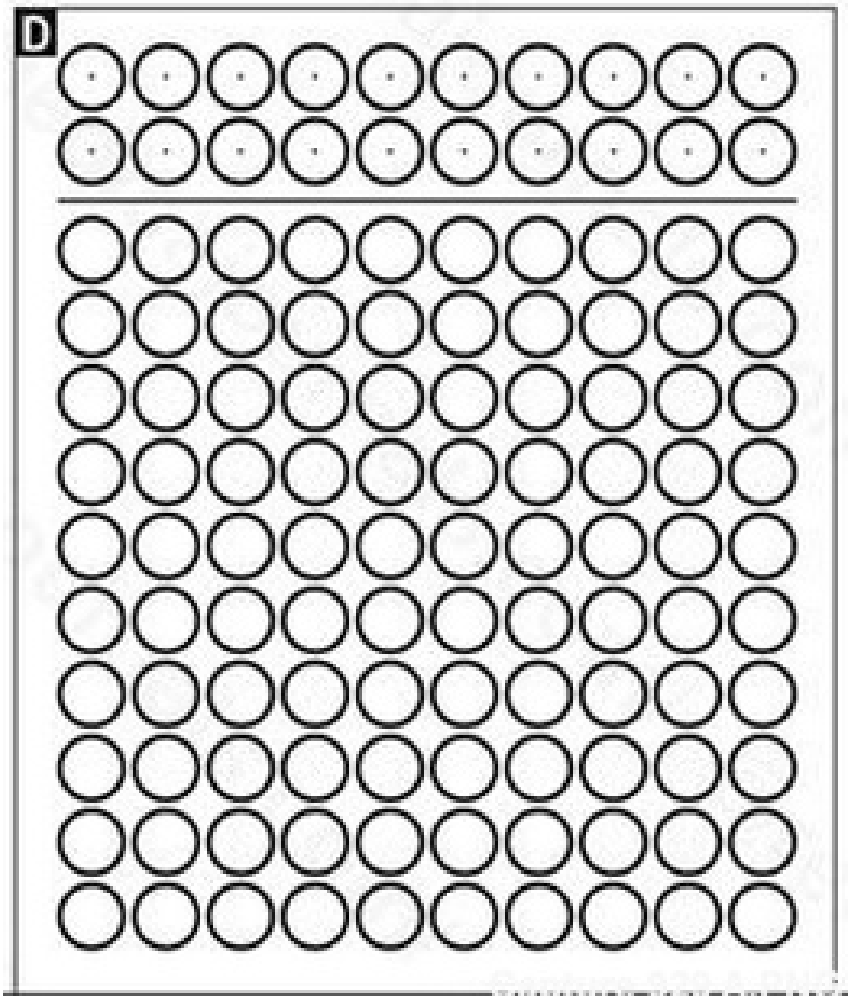


Figure 20. Digit symbol test.

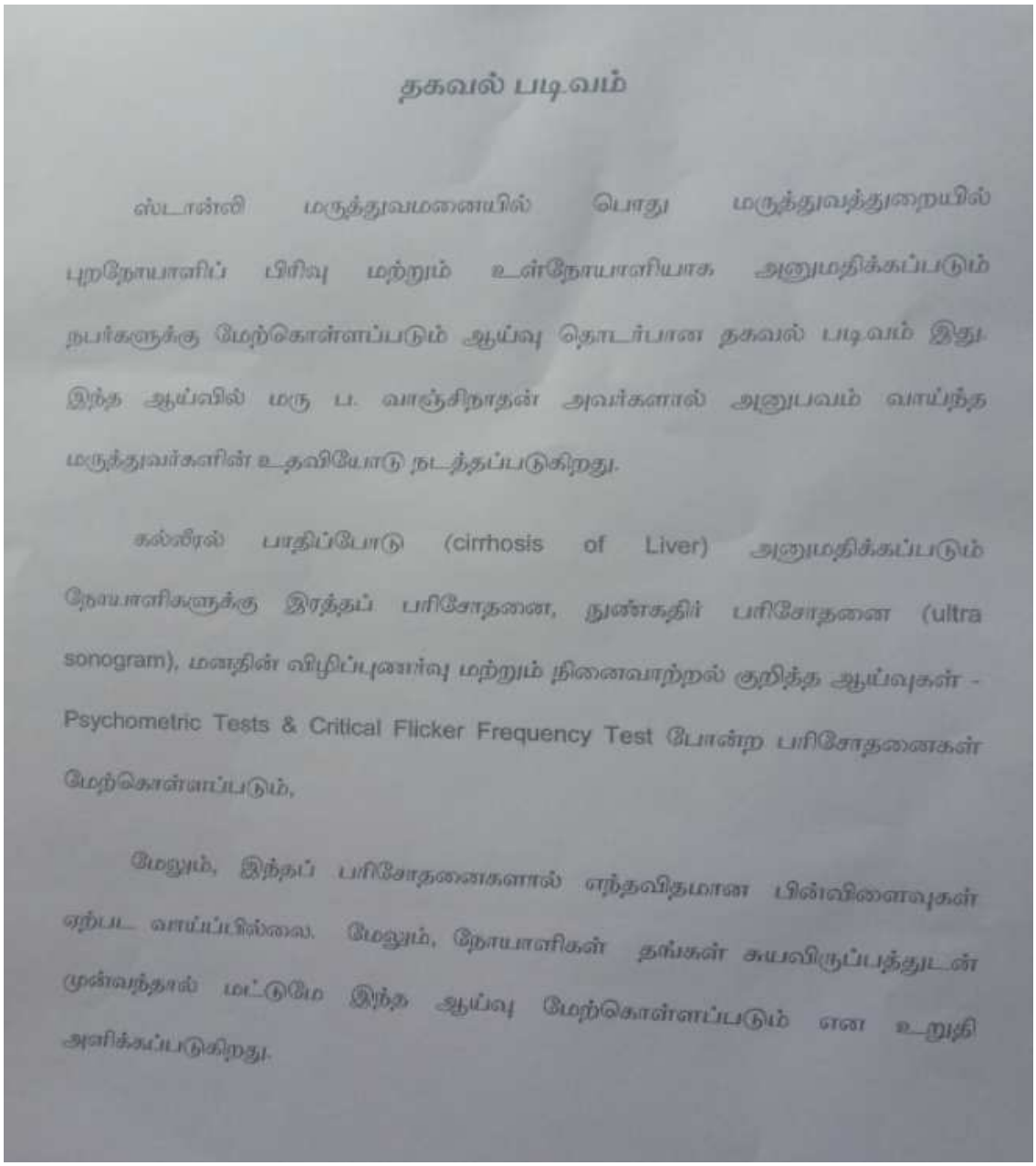
LINE TRACING TEST



SERIAL DOTTING TEST



CONSENT FORM



தகவல் படிவம்

ஸ்டான்லி மருத்துவமனையில் பொது மருத்துவத்துறையில் புறநோயாளிப் பிரிவு மற்றும் உள்நோயாளியாக அனுமதிக்கப்படும் நபர்களுக்கு மேற்கொள்ளப்படும் ஆய்வு தொடர்பான தகவல் படிவம் இது. இந்த ஆய்வில் மரு ப. வாஞ்சிநாதன் அவர்களால் அனுபவம் வாய்ந்த மருத்துவர்களின் உதவியோடு நடத்தப்படுகிறது.

கல்லீரல் பாதிப்போடு (cirrhosis of Liver) அனுமதிக்கப்படும் நோயாளிகளுக்கு இரத்தப் பரிசோதனை, நுண்கதிர் பரிசோதனை (ultra sonogram), மனதின் விழிப்புணர்வு மற்றும் நினைவாற்றல் குறித்த ஆய்வுகள் - Psychometric Tests & Critical Flicker Frequency Test போன்ற பரிசோதனைகள் மேற்கொள்ளப்படும்.

மேலும், இந்தப் பரிசோதனைகளால் எந்தவிதமான பின்விளைவுகள் ஏற்பட வாய்ப்பில்லை. மேலும், நோயாளிகள் தங்கள் சுயவிருப்பத்துடன் முன்வந்தால் மட்டுமே இந்த ஆய்வு மேற்கொள்ளப்படும் என உறுதி அளிக்கப்படுகிறது.

ETHICAL COMMITTEE APPROVAL LETTER

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : A Study on usefulness of psy chometric tests and critical flicker frequency in Diagnosis of minimal hepatic encephalopathy in patients with cirrhosis

Principal Investigator : Dr.P.Vanjinathan

Designation : PG in MD (Gen.Med)

Department : Department of General Medicine
Government Stanley Medical College,
Chennai-1

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 08.07.2013 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

10/10/13

KEY TO MASTER CHARTS

Bilirubin	**1=1-2mg/dl 2=2-3mg/dl**
Ascites	**1-Absent 2-Moderate 3-Severe**
Albumin	**1=>3.5mg/dl 2=3to3.5mg/dl 3=<3.0mg/dl**
Prothrombin time (PT) in sec	**1=1-4sec 2=4-6sec 3=>6sec**
Child Pugh's class (CPT)	**1=5,6 2=7,8,9 3= 10 to 15**
NCT-A NCT-B	**Number Connection Test –A , Number Connection Test -B**
DST	**Digit Symbol Test**
LTT	**Line Tracing Test**
SDT	**Serial Dotting Test**

ABBREVIATIONS

ACh	–	Acetyl Choline
BBB	–	Blood Brain Barrier
DST	–	Digit Symbol Test
EEG	-	Electroencephalogram
GABA	-	Gamma amino butyric acid
GCS	-	Glasscow Coma Scale
HE	–	Hepatic Encephalopathy
LFT	–	Liver Function Test
LTT	-	Line Tracing Test
MHE	–	Minimal Hepatic Encephalopathy
NCT	-	Number Connection Test
PT	-	Prothrombin time
SDT	–	Serial Dotting Test
USG	-	Ultrasonogram

MASTER CHART - CASES

SEX	Age	Hb gm%	Urea	Creat	Bilirub	Album	Ascites	PT	CPT CLASS	Alcoholic	Viral mar	NCT-A	NCT-B	DST	LTT	SDT	CFF (Hz)	CFF(SD)
M	32	10.6	26	0.6	1	1	1	1	1	YES	NEGATIVE	49	154	195	565	235	36.2	1.16
M	38	9.2	22	0.5	2	2	1	1	1	YES	NEGATIVE	50	166	206	675	79	46.6	2.1
M	68	10.2	30	1.1	3	3	3	3	3	YES	NEGATIVE	52	268	278	630	105	33.2	1.7
F	42	9.6	29	1	1	1	1	2	1	NO	NEGATIVE	48	152	236	645	125	31.4	1.05
F	42	9.1	26	8	1	2	1	2	1	NO	NEGATIVE	62	174	240	548	69	36.2	1.17
M	52	10.8	30	5	2	2	2	2	2	YES	NEGATIVE	54	162	192	622	275	35.1	1.7
F	37	10.2	28	1.1	4	3	3	3	3	NO	NEGATIVE	95	290	339	698	280	37	1.33
M	68	10.4	35	1	2	2	2	1	2	YES	NEGATIVE	58	168	186	720	295	30.9	1.61
M	56	9.8	33	0.7	1	1	1	2	1	YES	NEGATIVE	56	210	265	735	305	34.6	1.68
M	36	11.2	29	0.8	2	2	2	1	2	YES	NEGATIVE	95	242	275	536	235	32.4	1.11
M	69	9	37	1.2	3	3	3	3	3	YES	NEGATIVE	101	196	286	715	318	37.3	1.3
F	39	8.6	22	0.6	2	2	1	2	2	NO	HBV +	55	206	308	692	345	33.3	1.22
M	41	10.3	30	0.5	1	1	1	1	1	NO	HBV +	58	161	239	680	285	35.8	1.08
M	48	12	35	0.7	3	3	3	3	3	YES	HBV +	115	302	315	705	297	38.3	0.65
M	30	12.3	19	0.6	2	3	3	3	3	YES	HBV +	60	196	329	568	108	41.1	1.37
M	37	11.3	21	0.4	3	3	3	3	3	YES	HBV +	57	245	262	720	75	36.2	1.62
M	31	11.1	26	0.6	1	1	1	2	1	YES	HBV +	65	286	285	650	280	38.5	1.43
M	30	12.6	27	0.8	3	3	2	1	2	YES	HCV+	125	174	295	748	273	35.5	0.9
F	30	9.2	19	0.4	2	2	2	1	2	NO	HBV +	139	156	195	540	125	39.9	0.63
M	39	11.6	20	0.5	3	3	3	3	3	YES	HBV +	95	306	340	692	314	36.3	2.43
M	37	11.8	32	0.8	1	1	2	1	1	YES	HBV +	82	165	186	635	335	42.4	1.52
M	20	12.4	19	0.4	2	2	2	2	2	YES	HBV +	139	194	255	672	345	34.6	1.12

M	29	10.9	21	0.5	3	3	2	1	2	YES	HBV +	105	152	205	550	632	36.6	1.53
M	53	10.4	31	0.6	3	3	3	3	3	YES	HBV +	98	275	276	708	260	34.7	0.72
F	30	9.6	22	0.8	1	1	1	2	1	NO	HBV +	48	275	286	740	345	35.6	1.04
M	30	12.2	24	0.8	2	2	2	1	2	NO	HBV +	95	246	306	635	296	34	0.84
M	37	11.4	35	0.5	3	3	3	3	3	NO	HBV +	109	196	236	679	306	37.9	0.57
M	54	9.8	38	0.9	1	2	1	2	1	YES	HBV +	56	302	317	526	283	32.4	1.63
M	40	11	27	0.8	2	2	1	2	2	YES	HBV +	45	262	325	732	295	34.6	1.31
M	26	12.1	21	0.6	3	3	3	3	3	YES	HBV +	135	193	203	638	306	34	2.35
M	49	11.6	37	0.8	1	2	1	2	1	YES	HBV +	58	306	337	706	345	34.3	1.12
M	37	10.4	19	0.5	3	3	3	3	3	YES	HBV +	94	246	339	639	329	34.7	1.77
M	33	12.4	21	0.6	2	2	2	1	2	NO	HBV +	118	174	180	585	235	41.7	0.99
M	51	11.8	32	1	3	3	3	3	3	NO	NEGATIVE	140	305	252	710	292	36.5	1
M	38	9.8	25	0.8	1	1	1	2	1	NO	NEGATIVE	48	198	279	692	308	35.9	1.49
M	40	10.2	31	0.9	2	2	2	1	2	YES	NEGATIVE	138	286	251	572	210	37.9	0.41
M	33	11	29	0.8	3	3	2	1	2	YES	NEGATIVE	116	176	190	687	312	33.7	1.97
F	55	9	34	0.9	1	1	1	2	1	NO	NEGATIVE	51	254	306	725	285	37	2.31
F	50	9.6	32	1	2	2	2	1	2	NO	NEGATIVE	135	163	203	692	313	35.5	1.28
M	27	11.8	28	0.5	3	3	3	3	3	YES	NEGATIVE	106	236	318	585	178	41.3	0.78
M	61	10.6	38	1.2	1	1	1	2	1	YES	HCV+	88	278	329	710	348	36.4	1.24
M	53	11	34	0.9	2	2	1	1	1	YES	NEGATIVE	60	175	239	720	254	36.7	0.86
M	53	9.6	31	1	3	3	3	3	3	NO	NEGATIVE	117	304	330	684	336	33.8	1.41
F	45	8.6	33	0.7	1	1	1	2	1	NO	NEGATIVE	54	218	335	695	275	34.7	1
F	19	10.2	29	0.5	3	3	3	1	3	NO	WILSON'S	105	168	216	594	210	49.3	5.33
M	62	10.8	39	1.1	2	2	1	2	2	YES	NEGATIVE	56	230	265	736	280	33.3	1.21
M	45	11.4	29	0.9	1	1	1	2	1	NO	NEGATIVE	47	264	302	736	326	35.5	1.56
F	32	9.6	24	0.6	3	3	3	3	3	NO	NEGATIVE	104	295	295	675	315	36	0.97
M	50	11.6	31	0.7	2	2	1	2	2	YES	HBV+	51	304	316	605	228	39.9	1.02

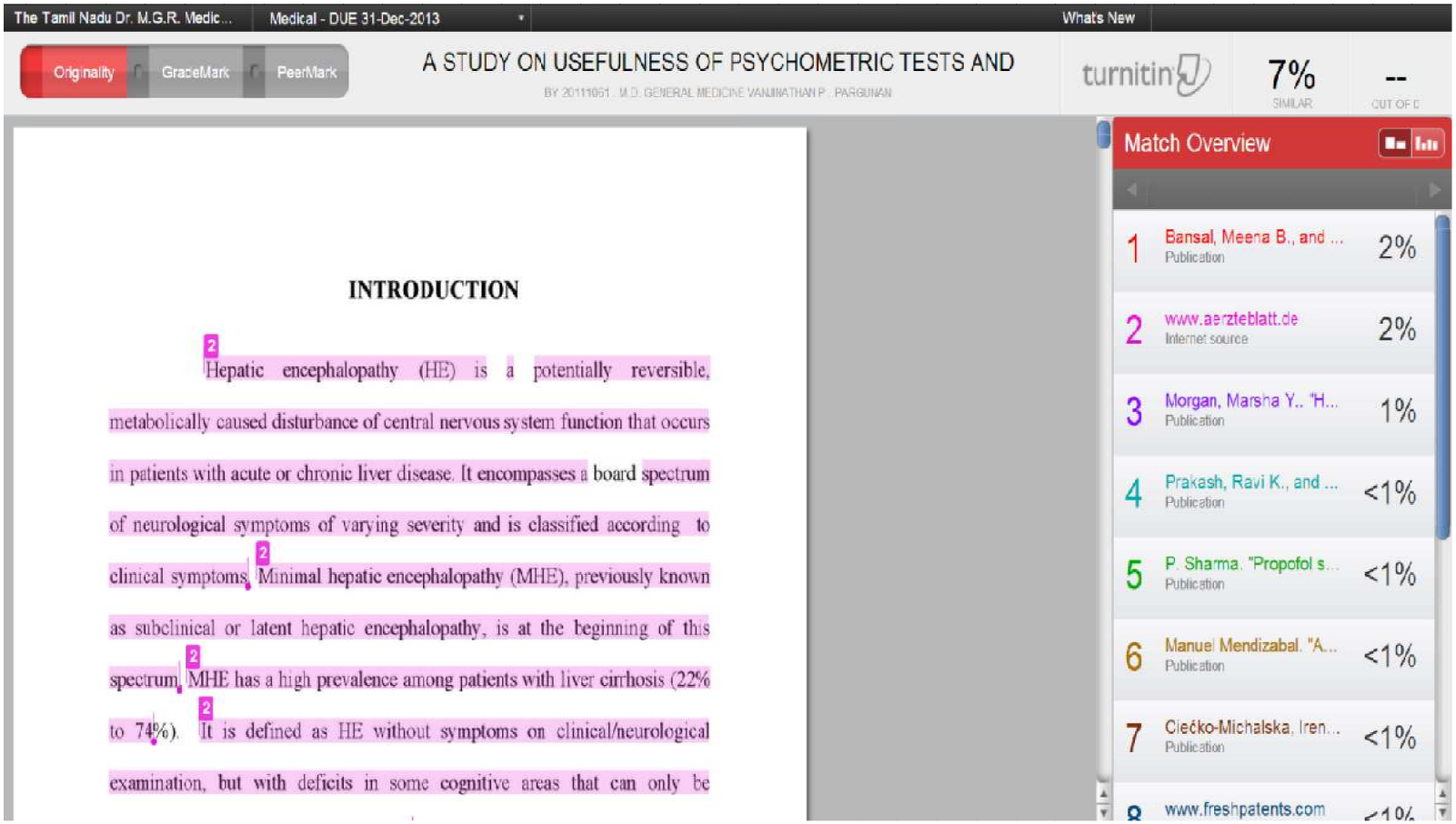
M	28	11.2	24	0.6	1	2	1	2	2	NO	HBV+	58	248	340	639	260	36.2	1.39
M	23	12.6	25	0.6	3	3	3	3	3	YES	HBV+	99	286	295	740	322	41.6	0.63
M	63	9.4	37	1.1	2	2	2	1	2	YES	HBV+	96	172	195	705	250	31.2	2.55
M	20	13.4	18	0.7	1	1	1	2	1	NO	HBV+	46	298	268	659	329	42.2	0.33
M	68	11	36	1.2	2	2	2	1	2	YES	HBV+	107	179	204	572	165	36.9	0.67
M	27	12.6	20	0.7	3	3	3	3	3	YES	HBV+	100	302	296	730	340	33.8	1.86
M	40	10.8	24	0.9	1	1	1	1	1	YES	HBV+	60	180	306	670	282	40.8	2.13
M	60	12	32	1	2	2	1	2	2	NO	HBV+	109	196	316	604	206	36.2	0.52
F	60	10.6	36	1.2	3	3	3	3	3	NO	HCV+	114	267	325	737	259	34.7	1.18
F	25	10.8	19	0.8	1	1	1	1	1	NO	HBV+	54	156	237	605	176	40.8	1.81
M	23	12.4	21	0.9	3	2	2	1	2	YES	HBV+	109	173	340	692	286	32.4	1.32
M	56	11.6	33	0.8	3	2	1	2	2	YES	HBV+	51	302	257	648	254	38.8	0.79
M	19	14.6	18	0.6	1	2	1	2	2	YES	HBV+	49	197	229	706	263	40.3	2.04
M	46	11.4	25	0.8	3	3	3	3	3	YES	HBV+	130	275	306	528	186	37	0.51
F	48	9.2	24	0.7	2	2	2	1	2	NO	HBV+	109	154	218	720	309	40.6	0.96
M	36	11.6	27	0.6	1	1	1	2	1	YES	HBV+	57	264	338	685	318	36.6	1.29
M	42	11	30	0.9	2	2	2	1	2	YES	HBV+	150	180	186	565	146	31	1.39
F	29	9.4	34	0.5	3	3	3	3	3	NO	HBV+	135	286	259	725	330	29.3	1.23
M	46	11.2	31	0.6	1	1	1	2	1	NO	HCV+	60	245	315	697	257	39.1	0.45
F	52	8.9	38	0.8	3	3	3	3	3	NO	HBV+	98	278	256	542	132	42.5	0.37
M	37	13.2	19	0.9	2	2	1	2	2	YES	HBV+	61	236	306	620	278	38.8	0.56
M	41	12.4	21	0.8	2	2	2	1	2	YES	HBV+	107	157	236	685	306	44.8	2.03
M	31	12.6	18	0.7	1	1	1	1	1	YES	HBV+	67	176	206	715	286	40.8	0.86
M	61	10.2	38	1.1	3	2	2	1	2	NO	HBV+	108	162	229	608	186	31.1	0.7
M	41	11.8	27	0.5	3	3	3	2	3	YES	HBV+	139	297	282	739	305	36.6	0.32
M	46	12.6	28	0.8	1	1	1	1	1	NO	HCV+	59	180	296	730	329	39.8	0.55
M	33	12	24	0.6	2	2	2	2	2	YES	HBV+	137	305	287	526	215	41.3	0.93

M	60	9.4	35	1.1	3	3	3	3	3	NO	HBV+	125	278	259	685	268	31.3	1.53
M	49	10.6	30	0.9	1	1	1	1	1	YES	HBV+	52	153	312	638	276	33.5	1.63
M	50	9.8	36	1	2	2	1	1	1	YES	HBV+	61	164	329	695	286	35.9	0.58
M	55	11.2	35	1.1	1	1	1	1	1	YES	HBV+	57	151	185	609	238	35.5	1.39
M	40	11	28	0.6	3	3	3	3	3	YES	HBV+	135	235	339	720	308	35.2	0.44
M	40	12.1	24	0.5	2	2	2	2	2	YES	HBV+	54	285	278	725	345	45.1	1
M	41	13	19	0.8	3	3	3	1	3	YES	HCV+	138	178	295	628	295	42.6	0.81
F	31	9.2	18	0.7	1	1	1	3	1	NO	HBV+	48	302	286	648	307	38.9	0.73
F	42	9.8	28	0.9	3	3	2	1	2	NO	HBV+	62	169	196	582	210	38.5	0.84
F	55	9	34	1	2	2	2	1	2	NO	HBV+	68	172	256	740	328	36.3	0.49
F	23	9.3	19	0.6	3	3	3	2	3	NO	HBV+	130	262	305	705	286	41.6	1.03
M	47	13	25	0.5	2	2	2	1	2	YES	HCV+	70	179	182	670	316	33.2	2.4
M	35	12.4	18	0.5	3	2	2	2	2	NO	HBV+	81	295	239	700	325	39.2	2.84
M	42	11.6	31	0.6	3	2	2	1	2	YES	HBV+	83	153	235	596	228	37.9	0.83
F	36	9.3	21	0.6	3	3	3	3	3	NO	HBV+	109	264	335	685	350	30.4	2.52
F	41	8.4	25	0.7	2	2	1	3	2	NO	HBV+	51	236	269	705	327	34.4	0.57
F	31	9.6	19	0.8	3	3	3	3	3	NO	HBV+	118	285	289	680	250	33.9	0.65
M	43	12.2	23	0.9	1	1	1	1	1	YES	HBV+	58	180	240	603	297	35.7	1.29
M	35	11.4	20	0.6	2	2	2	1	2	NO	NEGATIVE	71	173	306	692	296	36.9	1.22
F	22	9.6	18	0.5	3	3	3	1	3	NO	NEGATIVE	120	305	326	735	345	39.9	0.65
M	32	11.4	19	0.6	2	2	1	2	2	YES	NEGATIVE	76	292	286	740	260	39.1	0.6
M	20	11.8	18	0.5	2	2	2	1	2	YES	NEGATIVE	61	150	305	620	337	29.3	0.35
M	40	10.2	24	0.8	3	3	3	1	3	YES	NEGATIVE	128	161	186	583	162	37.6	1.62
M	38	11.6	22	0.9	3	2	2	1	2	YES	NEGATIVE	69	180	329	739	308	42.8	0.93

MASTER CHART -CONTROLS

SEX	AGE	NCT-A	NCT-B	DST	LTT	SDT	CFF (Hz)	CFF(SD)
M	32	56	129	180	525	206	52.6	1.2
M	38	60	136	175	539	148	50.1	0.64
F	42	46	175	215	540	235	46.2	0.76
M	64	54	179	210	532	175	46.2	1.24
M	52	50	165	145	605	162	38.2	1.2
F	43	55	125	240	635	182	41.2	0.64
F	37	78	165	145	582	192	45.6	2.14
M	56	60	136	156	575	235	48.2	1.76
M	36	86	145	168	602	140	50.2	0.74
M	69	56	156	172	608	158	53.9	0.82
M	39	74	176	192	582	162	44.2	0.46
F	27	48	125	205	610	185	46.8	0.7
M	30	50	135	238	589	196	47.2	1.9
M	37	56	140	150	537	210	39.2	1.43
M	31	64	152	171	558	235	53.8	0.63
F	30	58	165	176	542	240	51.2	0.52
M	39	53	176	182	564	146	45.3	1.68
F	20	60	179	206	575	178	48.2	2.34
M	29	58	129	235	582	196	51.2	1.9
F	50	52	134	182	536	185	38.2	1.87
M	22	78	142	202	594	840	53.9	1.44
F	38	48	149	260	702	215	45.2	0.66
F	54	54	172	235	535	183	38.9	1.42
M	40	60	165	220	560	216	49.2	2.8

M	26	56	154	152	601	239	51.2	1.6
M	49	54	138	164	609	168	53.4	1.9
F	30	66	167	168	521	182	45.2	1.46
F	38	48	157	172	562	196	50.1	0.86
M	51	52	178	185	549	208	52.6	0.62
F	38	57	159	205	610	231	46.4	1.6
F	40	58	180	201	539	152	44.6	1.21
M	33	56	120	150	581	159	48.1	1.96
F	55	74	127	159	590	230	46.9	2.9
F	51	51	132	168	606	219	37.2	1.61
M	38	49	167	172	529	149	51.6	0.62
M	42	56	158	195	531	230	53.4	0.94
M	33	52	121	228	576	151	45.3	1.72
F	55	48	138	276	571	226	47.2	1.48
M	50	57	145	146	523	238	46.1	0.69
F	27	54	165	157	582	168	41.2	2.86
F	61	56	179	235	596	192	51.3	1.74
M	53	51	172	172	528	228	53.9	0.63
M	45	50	165	210	592	152	46.2	3.24
F	55	58	132	181	535	235	53.4	0.97
F	19	54	127	217	568	182	52.4	1.92
M	45	84	134	284	680	235	51.6	0.73
F	47	59	180	210	587	168	46.2	1.76
F	32	49	172	235	608	205	48.2	0.84
M	28	50	129	182	592	168	52.3	3.16
F	23	56	171	239	605	239	53.2	1.94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INTRODUCTION
Hepatic encephalopathy (HE) is a potentially reversible, metabolically caused disturbance of central nervous system function that occurs in patients with acute or chronic liver disease. It encompasses a board spectrum of neurological symptoms of varying severity and is classified according to clinical symptoms. Minimal hepatic encephalopathy (MHE), previously known as subclinical or latent hepatic encephalopathy, is at the beginning of this spectrum. MHE has a high prevalence among patients with liver cirrhosis (22% to 74%). It is defined as HE without symptoms on clinical/neurological examination, but with deficits in some cognitive areas that can only be
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INTRODUCTION Hepatic encephalopathy (HE) is a potentially reversible, metabolically caused disturbance of central nervous system function that occurs in patients with acute or chronic liver disease. It encompasses a board spectrum of neurological symptoms of varying severity and is classified according to clinical symptoms. Minimal hepatic encephalopathy (MHE), previously known as subclinical or latent hepatic encephalopathy, is at the beginning of this spectrum. MHE has a high prevalence among patients with liver cirrhosis (22% to 74%). It is defined as HE without symptoms on clinical/neurological examination, but with deficits in some cognitive areas that can only be measured by...